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PERIARTERITIS NODOSA

A Case of Fatal Exfoliative Dermatitis Resulting from "Dilantin Sodium" Sensitization

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BALTIMORE
AND
C. ROWELL HOFFMANN, M.D.
CINCINNATI

THE TOXICITY of diphenylhydantoin sodium is well recognized and has been discussed in numerous reports.[1] Cutaneous reactions occur in 5 to 10 per cent of patients receiving therapeutic doses of the drug.[1a b] These reactions may be erythematous, scarlatiniform or morbilliform in character and may be accompanied with conjunctivitis and erosive lesions of the oral mucosa. Withdrawal of the drug usually results in rapid disappearance of the lesions. Exfoliative dermatitis is an occasional serious result of sensitization to diphenylhydantoin sodium ("dilantin sodium"),[2] but only one death clearly attributable to this was discovered in the literature.[3] The pathologic report in this case mentioned numerous hemorrhages in the skin, mouth, gastrointestinal tract and brain, fatty degeneration of the liver and congestion of the spleen.

The present case is of interest in that medication with diphenylhydantoin sodium was continued in the face of a cutaneous reaction and lesions of the mucous membrane. Fatal exfoliative dermatitis resulted, and at autopsy many granulomatous lesions were found in the skin, liver, spleen, kidneys and bone marrow. Many of these lesions were clearly a response to necrosis in the walls of arterioles and presented a clear picture of periarteritis nodosa.

From the departments of medicine and pathology of Baltimore City Hospitals.

1. (*a*) Kimball, O. P., and Horan, T. N.: The Use of Dilantin in the Treatment of Epilepsy, Ann. Int. Med. **13**:787,1939. (*b*) Merritt, H. H., and Putman, T. J.: Further Experience with the Use of Sodium Diphenyl Hydantoinate in the Treatment of Convulsive Disorders, Am. J. Psychiat. **96**:1023, 1940. (*c*) Finkelman, I., and Arieff, A. J.: Untoward Effects of Phenytoin Sodium in Epilepsy, J.A.M.A. **118**:1209 (April 4) 1942.

2. Mandelbaum, H., and Kane, L. J.: Dilantin Sodium Poisoning: Report of a Case with Dermatitis Exfoliativa, Pyrexia and Hepatic and Splenic Enlargement, Arch. Neurol. & Psychiat. **45**:769 (May) 1941.

3. Richie, E. B., and Kolb, W.: Reaction to Sodium Diphenyl Hydantoinate (Dilantin Sodium): Hemorrhagic Erythema Multiforme Terminating Fatally, Arch. Dermat. & Syph. **46**:856 (Dec.) 1942.

REPORT OF A CASE

W. G., a 71 year old Negro, was admitted to Baltimore City Hospital on April 13, 1946, in a stuporous state, with the primary complaint of an ulcerative stomatitis and conjunctivitis which could not be controlled by therapy in the patient's home.

Past History.—Except for exanthems in childhood and malaria during adolescence, the patient had always enjoyed good health. During the past two years he became aware of insidiously increasing nocturia, dribbling and incontinence. There was no history of cutaneous disease, hives, asthma or food or drug sensitivity. He had never had any head injuries, coma or convulsions. During the past five years the patient's family physician recorded normal blood pressures, and repeated physical examination had revealed little more than senility and peripheral arteriosclerosis. The prostate was soft and moderately enlarged.

There was no history suggestive of allergy or of epileptic attacks in the patient's family.

In November 1945 the patient had had three generalized convulsions, the first in his life, at about weekly intervals. They lasted several minutes, there was no incontinence or injury and, although the patient was slightly confused, they were not followed by stupor. The patient was treated with diphenylhydantoin sodium, 0.1 Gm. three times daily, by his family physician, with instructions to take the drug only to control convulsions. He had the prescription refilled and took the drug continuously until his admission to the hospital.

During January 1946, loss of appetite and dull pain in the upper abdominal area developed, and on several occasions the patient passed black stools and vomited small amounts of blood. These symptoms cleared when "creamalin" (aluminum hydroxide gel) was administered symptomatically. There was no recurrence.

During the last week of March 1946, he was seen by his physician to have a diffuse maculopapular rash, injection of the scleras and spots on the oral mucosa. This was considered to be measles, as a measles epidemic was present in the community. On April 7 an ulcerative stomatitis developed along the margins of the gums. This spread to the entire mouth and throat in spite of oral penicillin therapy. The patient had been unable to take food or fluids on any of the five days prior to admission.

Physical Examination.—The patient was a senile, moderately emaciated, stuporous Negro with considerable dehydration. The temperature, pulse, respiration and blood pressure were within normal limits. The skin was loose and moderately edematous, with pronounced loss of elasticity. Over the entire body small flakes were desquamating, and large sheets were peeling from the palms and soles. There were hard, shotty and discrete nodes in the left cervical area and bilateral inguinal adenopathy. The lids were matted with pus, and the scleras and conjunctivas were injected. There was grade I retinopathy. The nasal mucosa was moderately crusted. The mouth was filled with a thick yellow exudate, which on removal revealed the mucosa to be dehydrated and covered by confluent, indurated, necrotizing ulcers involving the lips, gums, alveolar margins, anterior pillars and palate. The tongue, tonsils and pharynx were not involved. There was notable hyperplasia of the gums around the few carious teeth present.

The chest was of emphysematous contour, with pulmonary fields uniformly hyperresonant to percussion. There was a small area of increased voice sound transmission over the left anterior side of the chest. Throughout the pulmonary fields the breath sounds were harsh and of a bronchial character, with coarse inspiratory

and expiratory rhonchi. The abdomen was normal. Rectal examination revealed a moderately enlarged prostate and large external hemorrhoids. The peripheral arteries were thickened and tortuous. The remainder of the physical examination revealed nothing abnormal.

Laboratory Data.—Routine specimens of urine were within normal limits. A moderate hypochromic microcytic anemia was present, with 3,200,000 erythrocytes, 8.5 Gm. of hemoglobin and a hematocrit value of 23.5. The corrected sedimentation rate (Wintrobe) was 12 mm. per hour. The white blood cell count was 6,100 with a normal differential count and no eosinophilia. Examination of the stool revealed no abnormalities. Roentgenologic examination of the lungs and pelvis revealed them to be normal. Other findings were without significance.

Hospital Course.—The patient was maintained with small feedings of a high protein and carbohydrate liquid diet, supplemented by parenteral administration of dextrose, "amigen" and vitamins to meet his fluid and caloric requirements. The

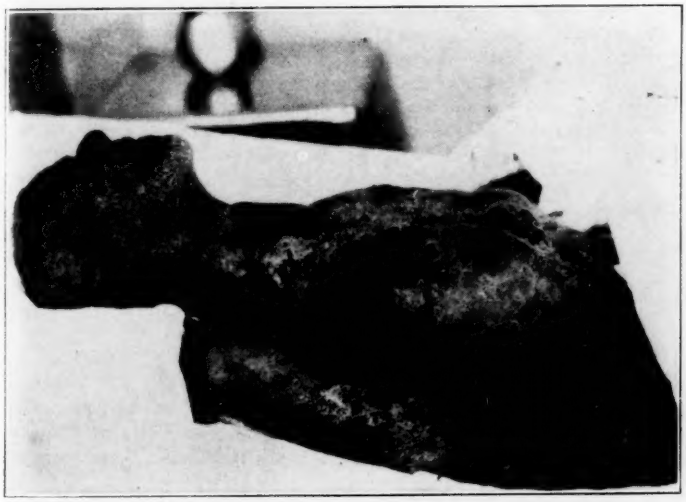


Fig. 1.—Photograph of the patient on the fourth day in the hospital.

mouth was irrigated with half strength hydrogen peroxide and the eyes treated with zinc sulfate and epinephrine drops. Penicillin, 40,000 units, was given every three hours.

Biopsy of an inguinal node on the fourth day showed considerable destruction of the normal architecture. The endothelial elements were extremely conspicuous, with capillary proliferation crowding out the lymphoid tissue. The tissue was infiltrated throughout with eosinophils. Pigmented macrophages were present in some areas. This was considered a reactive lymphadenitis secondary to the exfoliative dermatitis.

The patient's general condition remained unchanged. He remained semi-stuporous and did not gain ground. As the fluid balance became better, the mouth became cleaner, but the ulcers showed no evidence of healing. The skin continued to desquamate in increasingly large sheets (fig. 1). On the fifth

day in the hospital muscular twitchings were noted and the liver was felt several centimeters below the costal margin. On the ninth day the patient quietly died.

Autopsy.—An autopsy was performed forty hours after death. Large sheets of desquamating epithelium were present over the entire body. The eyes were matted shut with a purulent exudate. The mucous membrance of the oral cavity were denuded and covered with bloody purulent material. Hard, shotty nodes were felt in the superficial chains.

The bronchi contained a copious yellow purulent exudate, but there was no consolidation of the parenchyma; there was minimal pulmonary edema. The heart weighed 300 Gm. and exhibited moderate arteriosclerotic changes.

The liver was enlarged and weighed 1,350 Gm. The capsule was smooth, but the edges were blunted and the consistency doughy. The lobules were distinct but did not appear engorged. The spleen weighed 110 Gm. The capsule presented a mottled pink and white appearance. On section the parenchyma was firm and the trabeculae prominent.

The renal capsules were stripped with difficulty. The cortex of each kidney was thinned and the surface granular. No petechiae were seen on repeated section. The prostate was diffusely enlarged, and the right lobe contained an encapsulated hard mass. There were enlarged, soft, gray, lymph nodes in the mesenteries, retroperitoneal chains, and in the mediastinum.

The brain was examined in the neuropathology department of the University of Maryland by Dr. John A. Wagner. No gross or microscopic lesions were found other than moderate arteriosclerotic degeneration.

Microscopic Examination.—Lungs: The bronchi and the larger bronchioles contained aspirated mucus and an exudate rich in macrophages and eosinophils. Eosinophils constituted about 50 per cent of the leukocytes found in the postmortem clot in the larger vessels.

Heart: The myocardial fibers were separated by interstitial edema, but no scars or inflammatory lesions were visible in the sections cut.

Liver: There was diffuse cloudy swelling throughout the liver. The portal spaces were infiltrated with mononuclear cells and eosinophils. This infiltration was associated with necrosis of arterioles, and adjacent to the necrotic arterioles there were occasional minute granulomatous foci containing epithelioid cells, macrophages and eosinophils. Some of the parenchyma of the liver proximal to the most markedly involved periportal spaces was likewise necrotic.

Spleen: Many arterioles had partially or completely necrotic walls which were surrounded by eosinophils and mononuclear cells. Among the latter were epithelioid cells arranged in palisade fashion about the affected vessels. There were occasional giant cells. In addition, occasional small vessels contained thrombi, and there were many small foci of necrosis in the pulp. Some of the trabeculae were partially or completely necrotic, and some of these were infiltrated with inflammatory cells or surrounded by epithelioid cells.

Kidneys: Necrotizing inflammatory arterial and arteriolar lesions of the type seen in the liver and spleen were scattered diffusely throughout both kidneys (fig. 2). Some glomeruli were likewise involved in the necrotizing process and were invaded by macrophages and eosinophils. The tubular epithelium showed cloudy swelling, and some of the cells contained hemosiderin granules.

Skin: The sloughing of epidermis was limited to the cornified layer. There were focal accumulations of polymorphonuclear and mononuclear cells deep in the corium, with eosinophils in abundance. In this layer the connective tissue and small vessels were undergoing necrosis.

Bone Marrow: The marrow of the sternum and vertebrae was hyperplastic, with a preponderance of nucleated red cells and eosinophils. Few mature cells of the myeloid series were seen. Periarteriolar lesions of the type described previously were observed.

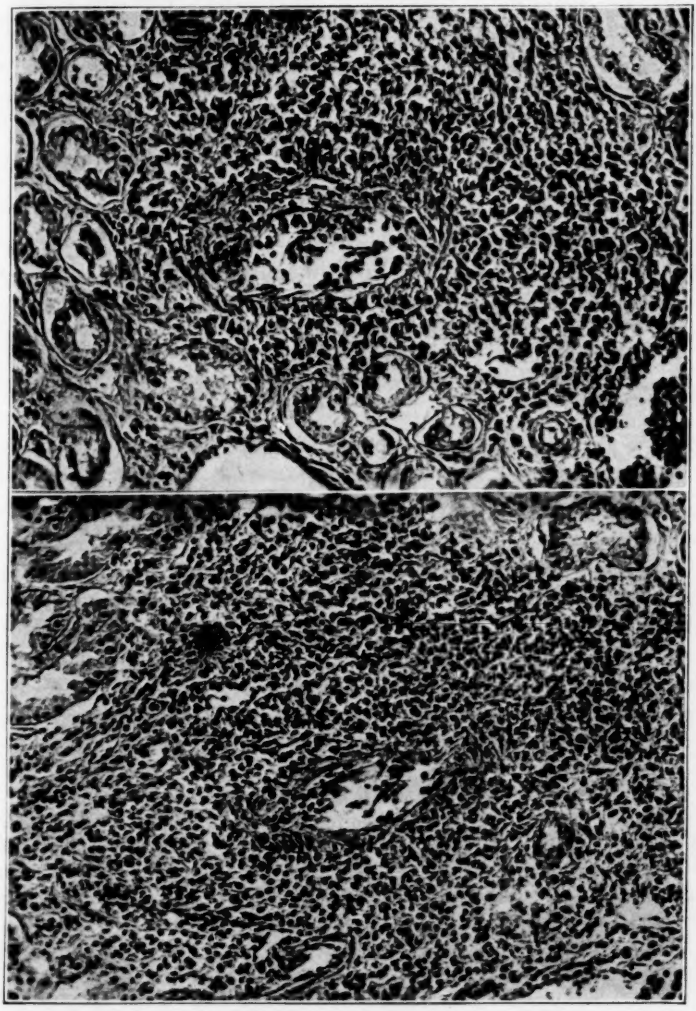
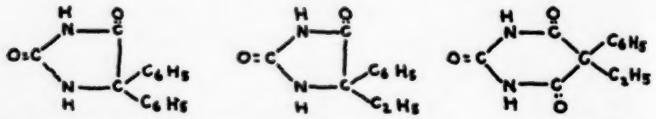


Fig. 2.—Photomicrographs of renal medulla showing necrosis of a small artery and arteriole. The cellular response is composed largely of mononuclear cells and eosinophils. Some of the cells surrounding the larger vessel have an epithelioid appearance and are beginning to orient in palisade fashion.

Other Organs: The pancreas, adrenals, stomach and intestine were free from the necrotizing process and exhibited no specific pathologic changes. The prostate was the site of benign hypertrophic changes and chronic inflammation. The lymph nodes did not differ from the one examined at biopsy.

COMMENT

The clinical reactions resulting from hypersensitivity to diphenylhydantoin sodium are similar to those resulting from sensitization to horse serum, the sulfonamide compounds, barbiturates, "nirvanol" (phenylethylhydantoin) and other drugs. The periarteriolar lesions in the present case are similar to those reported by Rich as occurring in human and experimental serum sickness and in hypersensitive reactions to sulfonamide drugs and to iodine.[4] These lesions are a manifestation of the anaphylactic type of hypersensitivity.[4b]



Dilantin (lactam form) Nirvanol Phenobarbital

Fig. 3.—Chemical composition of "dilantin" (lactam form), "nirvanol" and phenobarbital.

Ellis has emphasized the chemical kinship existing between dilantin sodium, "nirvanol" and phenobarbital.[5] Thus chemically, "dilantin sodium" is diphenylglycolyl urea, "nirvanol" is phenylethylglycolyl urea and phenobarbital is phenylethyl malonyl urea:

Of this group, "nirvanol" has fallen into disuse because "nirvanol sickness" was an almost constant result. However, as with "dilantin sodium," fatal exanthems were rare, and the vast literature on this drug contains no precise descriptions of the pathologic lesions.[6] Fatal reactions of this type due to the barbiturates, however, have been reviewed in several papers.[7] Although these cases were clinically similar to our case, no mention was made of periarteritis. It therefore remains to be

4. (*a*) Rich, A. R., and Gregory, J. E.: The Experimental Demonstration that Periarteritis Nodosa Is a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. **72**:65, 1943. (*b*) Rich, A. R.: Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, ibid. **71**:375, 1942; (*c*) Hypersensitivity to Iodine as a Cause of Periarteritis Nodosa, ibid. **77**:43, 1945.

5. Ellis, F. A.: Reactions to Nirvanol, Phenytoin Sodium, and Phenobarbital, South. M. J. **36**:575, 1943.

6. Goebel, F.: Fuer und wider die Nirvanolbehandlung der Chorea minor, Deutsche med. Wchnschr. **57**:1313, 1931. Madden, J. F.: Nirvanol Eruptions, Arch. Dermat. & Syph. **26**:1065 (Dec.) 1932.

7. Wile, U. J., and Benson, J. A.: Exfoliative Dermatitis Due to Phenobarbital with Fatal Outcome: Report of Two Cases, Ann. Int. Med. **13**:1243 (Jan.) 1940. Sexton, D. L.; Pike, G. M., and Neilson, A.: Exfoliative Dermatitis and Death Due to Phenobarbital, J.A.M.A. **116**:700 (Feb. 22) 1941.

shown whether drugs of this group, other than diphenylhydantoin sodium, are capable of producing periarteritis nodosa.

It is not to be expected that periarteritis nodosa will occur in all patients in whom hypersensitive reactions to a given drug develop. Only some of those in whom serum sickness or cutaneous reactions to the sulfonamide drugs develop become affected with periarteritis nodosa, and the same is true of animals subjected to experimental serum sickness.[4a b] It should be emphasized, however, that the continued administration of a drug after symptoms of hypersensitivity have appeared is fraught with danger.

SUMMARY

A case is described of a patient in whom fatal exfoliative dermatitis developed as a result of medication with diphenylhydantoin sodium continued in the face of clear evidences of hypersensitivity to this drug.

At autopsy, inflammatory-necrotizing arterial lesions of the type occurring in serum sickness and in hypersensitive reactions to the sulfonamide drugs and to iodine were present in the liver, spleen, kidneys, bone marrow and skin.

It is reemphasized that continued medication with diphenylhydantoin sodium and certain other drugs after clinical evidences of hypersensitivity have developed may lead to periarteritis nodosa.

FOOD PROTEIN CONSUMPTION IN GLOMERULONEPHRITIS

Effect on Proteinuria and the Concentration of Serum Protein

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AND
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SAN FRANCISCO

WITHIN the last decade, few studies have been made of the relationship of consumption of food protein to proteinuria and to concentration of serum protein in glomerular nephritis, although previously many such reports appeared in the literature. Additions to the knowledge of renal pathophysiology during this period, however, offer explanations for phenomena previously unexplained, and contradict some interpretations which have been offered in the past. Certain objections now may be made to the technic employed in some of the older investigations. The therapeutic corollary to this relationship still remains a source for controversy, but much evidence has accumulated to show that attempts at treatment with high protein diets in conditions associated with renal damage may not be helpful, as was previously supposed by some, but may be dangerous. For these reasons, the following experiments were undertaken to demonstrate the effect of varying levels of consumption of food protein on proteinuria and the concentration of serum protein in glomerular nephritis.

METHODS AND REPORTS OF CASES

For this study 2 patients in the degenerative stage of glomerular nephritis were selected. Both were excreting large quantities of protein in their urine, both had low concentrations of serum protein, and both were edematous.

CASE 1.—Mr. A. H., a white carpenter, aged 63, entered the medical ward of Stanford University Hospitals on Oct. 4, 1946, because of dyspnea and massive, generalized edema. For two years prior to admission, he had experienced increasing swelling of his lower extremities, scrotum, hands and face. Gradually in-

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Technical assistance was given by Mrs. Evalyn Barrett and Miss Helen J. Ureen.

From the Department of Medicine, Stanford University School of Medicine, San Francisco.

These experiments were aided by grants from the United States Public Health Service and the Columbia Foundation.

creasing dyspnea and fatigue first appeared eight months before entry. One previous examination of the urine in 1929 was said to have given negative results. No history was obtained of hematuria, other symptoms suggestive of renal disease, cough, orthopnea or pain in the chest.

Physical examination disclosed massive, soft, pitting edema of his lower extremities and scrotum, involving his hands and face to a lesser extent. His fundi showed moderate arteriosclerotic changes, several old retinal scars and a few small hemorrhages. Fluid was present in the right pleural cavity, and a few moist rales were heard at the bases of both lungs. The heart was moderately enlarged, no murmurs were heard, and the rhythm was regular. The blood pressure was 204 systolic and 120 diastolic. Abdominal examination revealed nothing abnormal except edema of the abdominal wall.

Laboratory examination revealed: red blood cells 4,590,000 per cubic millimeter, hemoglobin 70 per cent (Sahli), white blood cells 8,960 and a normal differential count, serum protein 4.62 Gm. per hundred cubic centimeters, serum creatinine 2.97 mg. and serum cholesterol 243 mg. The specific gravity of the urine was 1.015, the p_H6, protein 27.4 Gm. per twenty-four hours, fatty casts 5,000,000 per twenty-four hours, granular casts 1,000,000 per twenty-four hours, red blood cells 14,000,000 per twenty-four hours, white blood cells and epithelial cells 10,000,000 per twenty-four hours and many oval fat bodies. The phenolsulfonphthalein excretion was 18 per cent in two hours, venous pressure 10 cm. of water, circulation time (arm to tongue) 17 seconds and vital capacity 1.9 liters.

Case 2.—Mr. E. H., a white radio technician, aged 25, entered the medical ward of Stanford University Hospitals on Nov. 1, 1946, because of generalized edema. He had experienced no serious illnesses until 1941, when a severe sore throat associated with fever and cervical lymphadenopathy developed. After physical and laboratory examination in April, 1944, he was accepted for military service. On Oct. 1, 1944, he first noted swelling of his ankles, which rapidly progressed, so that he gained 25 pounds (11.3 Kg.) in one month. From then until entry generalized edema persisted, necessitating fourteen admissions to the hospital for relief of the anasarca with Southey tubes and other measures.

Physical examination showed a marked, generalized, soft, pitting edema of his face, hands, abdominal wall, sacrum and lower extremities. His fundi were normal. Fluid was present in both pleural cavities, but no rales were heard. His heart was not enlarged, there were no murmurs, and the rhythm was regular. His blood pressure was 144 systolic and 90 diastolic. His abdomen contained a moderate amount of fluid.

Laboratory examination revealed: red blood cells 3,450,000 per cubic millimeter, hemoglobin 68 per cent (Sahli), white blood cells 11,800, a normal differential count, serum urea 111.8 mg. per hundred cubic centimeters, serum creatinine 6.85 mg., serum protein 4.59 Gm. and serum cholesterol 547 mg. The specific gravity of the urine was 1.014, the p_H6, protein 13.5 Gm. per twenty-four hours, granular casts 700,000 per twenty-four hours, hyaline casts 300,000 per twenty-four hours, no renal failure casts, red blood cells 12,000,000 per twenty-four hours, white blood cells and epithelial cells 32,000,000 per twenty-four hours and many oval fat bodies.

Case 1 was studied for four consecutive weeks and case 2 for three consecutive weeks. No fever or other complication arose in either patient during the experimental period. The patients were allowed to eat without restriction during the weekends. Biochemical measurements

were made from Monday to Saturday of each week, during which time the patients received diets containing adequate calories and vitamins and a carefully calculated amount of protein. The protein content of the diets was varied at weekly intervals, and ranged from 0.2 Gm. to 2.5 Gm. of protein per kilogram of body weight. The diet containing 2.5 Gm. of protein per kilogram of body weight was not given to the second patient, as it was considered to be too risky in view of his retention of nitrogen. Specific food proteins were not studied.

The schedule for collection of blood and urine was identical during each week. Twenty-four hour urine collections were made from Monday to Wednesday. On Thursdays and Fridays, urine was collected as follows: 7 a.m.—12 noon, 12 noon—5 p.m., 5 p.m.—10 p.m., 10 p.m.—7 a.m. Blood samples were taken at the end of each urine collection period on Thursdays and Fridays, and on Saturday mornings.

Effect of Food Protein Consumption on Serum Concentrations of Urea and Creatinine

Food Protein Consumption Gm./Kg. Body Wt./Day.	Case No. 1		Case No. 2	
	Serum Urea Mg./100 Cc.	Serum Creatinine Mg./100 Cc.	Serum Urea Mg./100 Cc.	Serum Creatinine Mg./100 Cc.
0.5	31.4	2.05	119.3	7.13
1.5	72.6	2.41	143.2	7.30
2.5	114.0	2.79	.....	....
0.2	45.5	2.42	122.9	7.22

Serum protein was determined by the copper sulfate method of Phillips and others,[1] this being checked frequently by a modification of the biuret method of Kingsley.[2] The urinary protein was measured by the biuret method.

RESULTS

The effects of consumption of different amounts of food protein on proteinuria and on the serum protein concentration are presented graphically in chart 1 for the patient in case 1 and in chart 2 for the patient in case 2.

1. Phillips, R. A.; Van Slyke, D. D.; Dole, V. P.; Emerson, K., Jr.; Hamilton, P. B., and Archibald, R.: Copper Sulphate Method for Measuring Specific Gravities of Whole Blood and Plasma, New York, The Josiah Macy, Jr., Foundation, February 1945.

2. Kingsley, G.: The Determination of Serum Total Protein, Albumin and Globulin by the Biuret Reaction, J. Biol. Chem. **131**:197-200 (Nov.) 1939.

Proteinuria.—In both cases alterations in the amount of food protein consumed were followed by parallel changes in the quantity of protein excreted in the urine. When the dietary protein was increased, the proteinuria was augmented. Similarly, decreasing the amount of dietary protein resulted in a diminished proteinuria. While these changes in excretion of protein were apparent on the first day of each new level

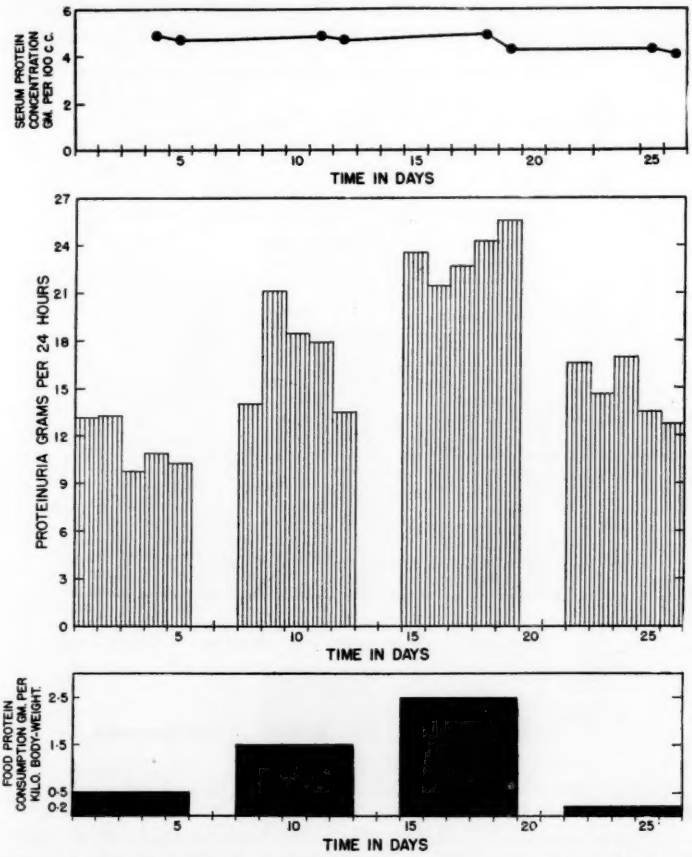
SERUM PROTEIN CONCENTRATION GM. PER 100 C.C.
TIME IN DAYS
PROTEINURIA GRAMS PER 24 HOURS
TIME IN DAYS
FOOD PROTEIN CONSUMPTION GM. PER KILO. BODY-WEIGHT.
TIME IN DAYS

Chart 1 (case 1).—Effect of consumption of food protein on proteinuria and concentration of serum protein.

of food protein consumption, they were not maximum until the new diet had been given for several days. This lag effect is particularly well illustrated in chart 2, when the dietary protein was changed from 1.5 Gm. to 0.2 Gm. per kilogram of body weight.

Diurnal Variations in Proteinuria.—The diurnal variations in proteinuria are shown in chart 3 for patient 1 and in chart 4 for patient 2.

In both cases more protein was excreted during the day than at night, the greatest proteinuria occurring during the morning and early afternoon. This variation was independent of the food protein consumed, as similar changes occurred at each level of protein intake.

Concentration of Serum Protein.—The concentration of serum protein was unaltered while the patients received nutritionally adequate amounts of dietary protein. Raising the protein intake above 0.5 Gm. of protein per kilogram of body weight did not increase the concentration of serum protein. During the week when the food protein consumed by patient 2 was reduced to 0.2 Gm. per kilogram of body weight, an inadequate amount, the concentration of serum protein diminished.

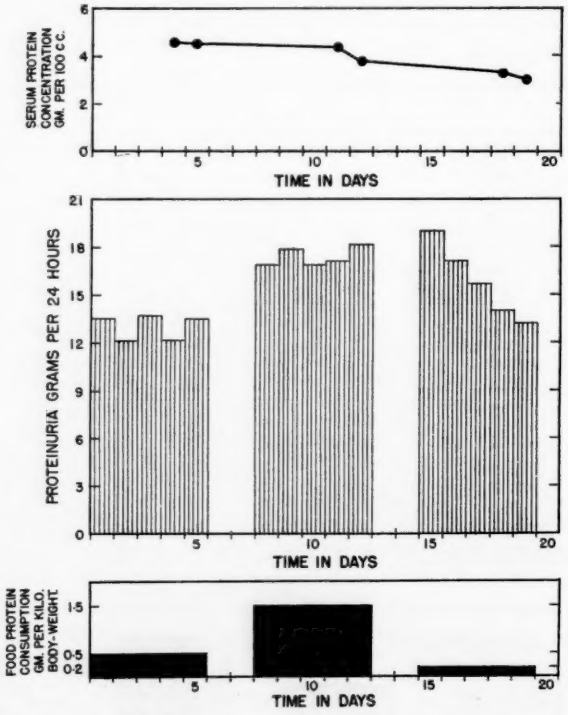

Chart 2 (case 2).—Effect of consumption of food protein on proteinuria and concentration of serum protein.

COMMENT

Berglund and associates and others described a parallel relationship between the amount of protein consumed and the amount of protein excreted in the urine.[3] All patients except 1 reported on by these in-

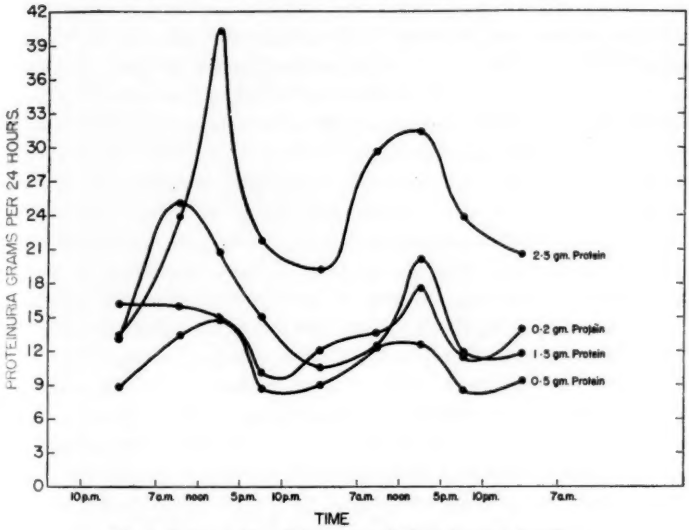

Chart 3 (case 1).—Diurnal variations in proteinuria.

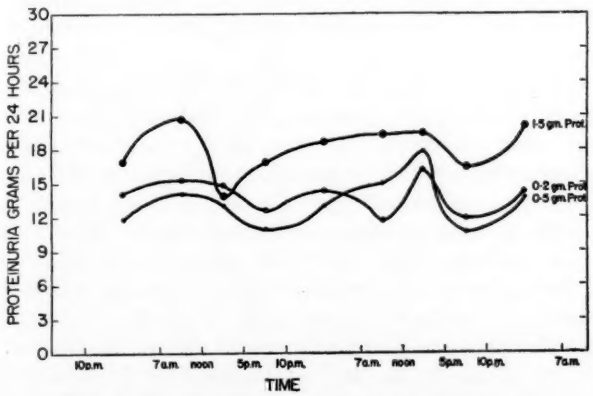

Chart 4 (case 2).—Diurnal variations in proteinuria.

vestigators excreted large amounts of protein while they were studied, as were the 2 patients presented here. Keutmann and McCann,[4] however,

3. (*a*) Bulger, H. A.: Studies of Hypoproteinemia and Proteinuria, J. Clin. Investigation **14**:705 (Sept.) 1935. (*b*) Keutmann, E. H., and Bassett, S. H.: Dietary Protein in Hemorrhagic Bright's Disease: II. The Effect of Diet on Serum Proteins, Proteinuria and Tissue Proteins, J. Clin. Investigation **14**:871-888 (Nov.) 1935. (*c*) Keutmann, E. H., and Bassett, S. H.: Studies on the Mechanism of Proteinuria, ibid., **16**:767-776 (Sept.) 1937. (*d*) Berglund, H.; Scriver, W., and Medes, G.: Proteinuria and Plasma Proteins, in the Kidney in Health and Disease, Philadelphia, Lea & Febiger, 1935, pp. 473-530.

4. Keutmann, E. H., and McCann, W. S.: Dietary Protein in Hemorrhagic Bright's Disease: I. Effects upon Course of the Disease, with Special Reference to Hematuria and Renal Function, J. Clin. Investigation **11**:973-994 (Sept.) 1932.

found this relationship in only 2 of 4 patients, and the increases in proteinuria during periods of high protein intake in these 2 patients were not large. Three of the 4 patients studied by them were excreting less than 1 Gm. of protein daily, and the proteinuria of the fourth patient rapidly diminshed from 2 Gm. daily. Liu and Chu[5] measured the protein excretion in 1 of the 2 cases they discussed, and they thought that the proteinuria did not vary significantly when the dietary protein was altered. This patient was excreting over 1 Gm. of protein daily, but the study was complicated by a variety of diseases, including gonorrhea, ankylostomiasis, ascariasis, and syphilis which required weekly injections of neoarsphenamine. It is well known that proteinuria often is influenced by concurrent diseases and surgical procedures. Furthermore, when a patient excretes less than 1 Gm. of protein daily, a variation of a few hundred milligrams represents a large proportional change. These small actual differences in proteinuria in patients with glomerular nephritis in the latent stage frequently are observed, even when a constant intake of protein is maintained. It is thought that such factors may have obscured the influence of consumption of food protein on proteinuria in these experiments. Without presenting adequate proof, Epstein[6] has stated that increasing dietary protein does not result in an augmented proteinuria.

The rise in proteinuria which follows an elevation in protein intake has been attributed to an increase in glomerular filtration which occurs when the dietary protein is increased.[3bc] Keutmann and Bassett[3c] induced such an effect by administering theobromine and urea as diuretic drugs. It is generally thought that diseased glomeruli allow serum protein to leak out through abnormal "pores" of various sizes, and that an increased renal blood flow presents more blood to these "pores." In this way, it is supposed that more protein will be filtered and increased proteinuria will be produced. While this explanation may be valid, additional factors may be involved. Since the observations of Ekehorn[7] and Richards, Bordley and Walker,[8] much evidence has accumulated to show that normal glomerular filtrate contains protein, and

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5. Liu, S. H., and Chu, H. I.: An Optimal Diet in Promoting Nitrogen Gain in Nephrosis, J. Clin. Investigation **14**:293-303 (May) 1935.

6. Epstein, A. A.: Further Observations on the Nature and Treatment of Chronic Nephrosis, Am. J. M. Sc. **163**:167-186 (Feb.) 1922.

7. Ekehorn, G.: Principles of Renal Function, Acta med. Scandinav., 1931, supp. 36, pp. 1-717.

8. Richards, A. N.; Bordley, J., III, and Walker, A. M.: Quantitative Studies of the Composition of Glomerular Urine, J. Biol. Chem. **101**:179-191 (June) 1933.

9. Walker, A. M., and Oliver, J.: Methods for Collection of Fluid from Single Glomeruli and Tubules of Mammalian Kidney, Am. J. Physiol. **134**:562-579 (Oct.) 1941. Addis, T.: Proteinuria, Tr. A. Am. Physicians **57**:106-108, 1942.

that protein is reabsorbed by the tubule cells. This hypothesis is based on physiologic,[9] morphologic[10] and clinical data.[11] Dock,[12] Gérard[13] and Oliver[14] have discussed this subject further. Therefore, it seems reasonable to suppose that the changes in proteinuria which occur when the dietary protein is altered are dependent not only on glomerular permeability and the rate of glomerular filtration, but also on the rate of tubular reabsorption of protein.

The delay in attainment of maximum change in proteinuria after the dietary protein is altered, or the lag effect, has been noted before by Keutmann and Bassett.[3b c] This effect is in contrast to the immediate increase in proteinuria which follows the intravenous administration of plasma protein. The investigations of Addis, Poo, and Lew[15] indicate that within the body there is protein which is readily available for use under certain conditions. Keutmann and Bassett suggested that ingested protein first must be converted to a form from which plasma protein may be synthesized, presumably in depots of labile protein. The necessary time for this to occur, and then to be reflected in a change in the rate of excretion of protein, was offered as an explanation for the lag effect. Since the concentration of plasma protein remains unchanged, may it not be supposed that an equilibrium exists between the level of food protein consumed, the activity of the mechanism by which plasma protein is made and the rate of excretion of protein in the urine?

The diurnal variations in proteinuria noted in these experiments were similar to those observed by Keutmann and Bassett,[3c] an increased proteinuria occurring during the waking hours. These variations probably arise because of simultaneous changes in renal blood flow, due to changes in posture, activity, body temperature, ingestion of food and fluid and other factors.

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10. Randerath, E.: Die Entwicklung der Lehre von den Nephrosen in der pathologischen Anatomie, Ergebn. d. allg. Path. u. path. Anat. **32**:91-140, 1937. Smetana, H., and Johnson, F. R.: The Origin of Colloid and Lipoid Droplets in the Epithelial Cells of the Renal Tubules, Am. J. Path. **18**:1029-1046 (Nov.) 1942.

11. Addis, T.: Renal Degeneration Due to Protein Reabsorption by the Kidney, Stanford M. Bull. **3**:67-69 (May) 1945.

12. Dock, W.: Proteinuria and Associated Renal Changes, New England J. Med. **227**:633-636 (Oct. 22) 1942.

13. Gérard, P.: Comparative Histophysiology of the Vertebrate Nephron, J. Anat. **70**:354-379 (April) 1936.

14. Oliver, J.: New Directions in Renal Morphology: Method, Its Results and Its Future, in The Harvey Lectures, 1944-1945, Lancaster, Pa., Science Press Printing Company, 1945, pp. 102-155.

15. Addis, T.; Poo, L. J., and Lew, W.: Protein Loss from Liver During a Two Day Fast, J. Biol. Chem. **115**:117-118 (Aug.) 1936.

16. Footnote 3*a* and *b*. Footnote 4.

The lack of change in the concentration of serum protein during these experiments corroborates the findings of many other investigators.[16] McDonald, Corcoran and LeFevre have noted that a high protein diet cannot be expected to correct that part of the hypoproteinemia due to the underlying renal lesion.[17] Nevertheless, Epstein[6] and more recently Peters and his associates[18] have suggested high protein diets for the treatment of nephritis, supposing that the concentration of serum protein might rise eventually. This concentration sometimes does rise during the course of the disease, but it may also fall, and this change is independent of the level of food protein consumed, providing that this level represents an adequate amount. In patients on a constant protein intake, a change in the concentration of serum protein may be associated with the advent of some infectious disease, with a change from one stage in the disease to another, and it may sometimes occur inexplicably. These facts are abundantly supported by much experimental evidence and are attested to by everyday experience in the clinic for renal disease of this hospital.

The cause of the hypoproteinemia still is not understood completely. Linder and his collaborators found that hydremic plethora does not occur in nephritis, and that the low concentration of serum protein cannot be accounted for by dilution.[19] The loss of protein in the urine obviously imposes an abnormal burden on the process by which plasma proteins are produced, but it does not appear to be solely responsible for the hypoproteinemia. This opinion is in accord with the conclusions of Bloomfield,[20] who reviewed various clinical and experimental conditions associated with hypoproteinemia. Using a mixed diet low in protein, he was unable to induce a lasting hypoproteinemia in rats, even though they lost weight and showed signs of malnutrition. If the diet is adequate in its various components, it cannot be supposed that the low concentration of serum protein reflects a deficiency state. Defective absorption of protein from the gastrointestinal tract has not been proved. Abormal formation of protein, however, may occur.

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17. McDonald, R. H.; Corcoran, A. C., and LeFevre, F.: Edema: III. Treatment, Cleveland Clin. Quart. **14**:20-27 (Jan.) 1947.

18. Peters, J. P.; Bruckman, F. S.; Eisenman, A. J.; Hald, P. N., and Wakeman, A. M.: The Plasma Proteins in Relation to Blood Hydration: VI. Serum Proteins in Nephritic Edema, J. Clin. Investigation **10**:941-973 (Oct.) 1931.

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20. Bloomfield, A. L.: The Effect of Restriction of Protein Intake on the Serum Protein Concentration of the Rat, J. Exper. Med. **57**:705-720 (May) 1933.

21. Footnote 18. Peters, J. P.; Bruckman, F. S.; Eisenman, A. J.; Hald, P. M., and Wakeman, A. M.: The Plasma Proteins in Relation to Blood Hydration: IX. Serum Proteins in the Terminal Stages of Renal Disease, J. Clin. Investigation **11**:113-122 (Jan.) 1932.

Muscular wasting is often associated with renal disease,[21] even when more than enough calories and protein are supplied in the diet. It is generally believed that the drop in the concentration of serum protein is mainly at the expense of the albumin fraction. Changes in the globulin fraction also have been observed.[22] Jameson[22b] has demonstrated electrophoretically that the serum of patients in the degenerative stage of glomerular nephritis contains a protein fraction which does not occur in normal serum. It seems likely that protein metabolism, particularly the mechanism for production of plasma protein, is altered qualitatively and quantitatively. The hypoproteinemia, the production of unusual plasma protein fractions and the muscular wasting all may depend partly on changes in the rate of protein synthesis and changes in the quality of the proteins synthesized.

THERAPEUTIC IMPLICATIONS

The dietary treatment of glomerular nephritis has evoked much discussion in the past. It has been demonstrated here, as well as in other investigations, that a higher than adequate protein intake does not elevate the serum protein concentration, and that it does increase the rate of excretion of protein in the urine. The increased proteinuria is accompained by an increase in urea clearance[3c] and is thought by some to be harmless to the kidneys. It may, however, further tax the protein reabsorptive ability of the tubule cells, this capacity already having been exceeded. Furthermore, an added burden may be placed on the mechanism for the production of plasma proteins, which also may be functioning imperfectly under stress.

When more dietary protein is consumed than can be utilized for anabolic purposes, the excess is deaminized to form urea. Borsook and Winegarden,[23] Addis,[24] and Newburgh[25] have shown that kidney work is dependent preponderantly on the urea content of the urine. The value

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22. (*a*) Kendall, F. E.: Studies on Serum Proteins, J. Clin. Investigation **16**:921-931 (Nov.) 1937. (*b*) Jameson, E.: Serum Protein Changes Occurring in Degenerative Stages of Bright's Disease, Proc. Soc. Exper. Biol. & Med. **36**:808-812 (June) 1937.

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24. Addis, T.: The Osmotic Work of the Kidney and the Treatment of Glomerular Nephritis, Tr. A. Am. Physicians **55**:223-229, 1940; The Treatment of Chronic Renal Insufficiency, J. Urol. **41**:126-136 (Feb.) 1939.

25. Newburgh, J. D.: The Changes Which Alter Renal Osmotic Work, J. Clin. Investigation **22**:439-446 (May) 1943.

26. Addis, T.: Glomerular Nephritis, New York, The Macmillan Company, 1948. Lippman, R. W., and Persike, E. C.: The Ambulatory Management of Azotemia and Clinical Uremia, Arch. Int. Med. **80**:579-586 (Nov.) 1947.

of reducing kidney work to a minimum in conditions associated with loss of nephrons has been demonstrated repeatedly, both in patients[26] and in experimental animals.[27] The concentrations of urea and creatinine in the serum frequently are used as indexes of renal failure. The complete data will be reported later, but average values for these substances and their relation to different levels of consumption of food protein for the 2 patients described here are presented in the table. These figures clearly show that increasing the consumption of food protein served to elevate the serum urea and creatinine concentrations, and thus induced an intensified azotemia.

In view of these considerations, it seems not only logical but necessary to prescribe not more than the minimum adequate amount of dietary protein. Formerly, the accepted figure was 1 to 1.5 Gm. of protein per kilogram of body weight per day. Sherman and his associates,[28] however, have established the requirement to be 0.5 Gm. per kilogram of body weight per day, and Hegsted and others[29] have given evidence that it may be even lower. For these reasons, we believe that patients who have lost renal tissue should eat a minimum but adequate amount of protein, and that as a rule this quantity should consist of 0.5 Gm. of protein per kilogram of body weight per day, plus an increment equal to that amount of protein lost in the urine.

SUMMARY

1. The proteinuria and the concentrations of serum protein of 2 patients in the degenerative stage of glomerular nephritis were compared in their relation to different levels of consumption of food protein.

2. Increasing the protein intake augmented the proteinuria but did not change the concentration of serum protein.

3. The significance of these effects and their therapeutic implications are discussed.

4. In conditions associated with loss of renal tissue, a diet containing a minimum but adequate amount of protein is recommended.

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27. Addis, T.; Barrett, E.; Lew, W.; Poo, L. J., and Yuen, D. W.: Danger of Intravenous Injection of Protein Solutions After Sudden Loss of Renal Tissue. Arch. Int. Med. **77**:254-259 (March) 1946. Farr, L. E., and Smadel, J. E.: Influence of Diet on the Course of Nephrotoxic Nephritis in Rats, Proc. Soc. Exper. Biol. & Med. **36**:472-473 (May) 1937; Effect of Dietary Protein on the Course of Nephrotoxic Nephritis in Rats, J. Exper. Med. **70**:615-627 (Dec.) 1939.

28. Sherman, H. C.; Gillett, L. H., and Osterberg, E.: Protein Requirement of Maintenance in Man and the Nutritive Efficiency of Bread Protein, J. Biol. Chem. **41**:97-109 (Jan.) 1920.

29. Hegsted, D. M.; Tsongas, A. G.; Abbott, D. B., and Stare, F. J.: Protein Requirements of Adults, J. Lab. & Clin. Med. **31**:261-284 (March) 1946.

COMPLEMENT FIXATION REACTIONS IN PSITTACOSIS

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DURING the course of investigations on the psittacosis-lymphogranuloma venereum group of diseases, an opportunity was afforded to test the fixation of complement in a number of samples of serum in the presence of psittacosis antigen. These samples were submitted by practicing physicians from patients suspected of having psittacosis. For persons whose serum reacted positively, clinical and epidemiologic data were requested and additional serum specimens tested when possible. The results of the complement fixation studies supplemented by the clinical and epidemiologic data form the basis of this report on 21 cases, the disease in none of which was fatal.

Psittacosis is a severe acute infectious disease manifesting itself principally as pneumonitis and characterized by headache, malaise, dry nonproductive cough, chills and usually physical signs of pneumonia. It is contracted by association with birds of various species, chiefly those of the parrot group and pigeons, which are infected with the specific virus. Although the disease usually occurs sporadically or in small household outbreaks, in 1929-1930 an unusual number of cases was reported throughout the world, with a recorded fatality rate of 17 to 36 per cent.[1] The disease contracted from pigeons or nonpsittacine birds sometimes is called "ornithosis"[2] and is similar clinically to psittacosis, but in experimental animals the pigeon virus appears to show some slight differences from strains recovered from parrots.[3] In the laboratory, psittacosis virus can be recovered by injecting into white mice inoculums of the sputum, organs and occasionally the blood of persons ill or dead of the disease. The characteristic clusters of elementary bodies (L.C.L. bodies) are seen in the infected organs of animals or human beings when stained with Giemsa's or Machiavello's stain. Antibodies are produced

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From the Division of Infectious Diseases, National Institute of Health.

1. Meyer, K. F.: The Ecology of Psittacosis and Ornithosis, Medicine **21**:175, 1942.

2. Meyer, K. F.; Eddie, B., and Yanamura, H. Y.: Ornithosis (Psittacosis) in Pigeons and Its Relation to Human Pneumonitis, Proc. Soc. Exper. Biol. & Med. **49**:609, 1942.

3. Beck, M. D.; Eaton, M. D., and O'Donnell, R.: Further Laboratory Studies on the Classification of Psittacosis-Like Agents, J. Exper. Med. **79**:65, 1944.

in the patients' serum which can be detected by the complement fixation test as first described by Bedson[4] and developed further by others.[5] It is noteworthy that because of a common group antigen, serum from persons infected with lypmphogranuloma venereum fixes complement in the presence of psittacosis and other antigens of this group. Therefore, the complement fixation reaction, while specific for the group, cannot be differentiated in the different diseases caused by the various viruses of the group.[6]

In the differential diagnosis, psittacosis must be distinguished from primary atypical pneumonia, which it resembles in its clinical manifestations, although it is usually severer. Recovery of the psittacosis virus from the patient or serologic evidence is the only reliable differentiation between them. Q fever of rickettsial origin also resembles psittacosis in its milder form and can be distinguished by virus isolation or specific serologic reactions. Other acute infections, such as influenza, typhoid and bacterial bronchopneumonia, are more easily recognized on clinical evidence, though often confused with psittacosis. The specific diagnosis of psittacosis is particularly important because of the apparent efficacy of penicillin in the treatment of the disease.[7] The unqualified laboratory diagnosis of psittacosis can be made only by the isolation from the patient and identification of the specific virus. Since the opportunity for such studies is not always available, the complement fixation reaction, when carefully interpreted, is useful in furnishing a basis for a diagnosis of reasonable certainty.

In this series of cases, the complement fixation tests were performed with an antigen prepared from the yolk sac or the allantoic fluid of the developing chick embryo infected with a strain of psittacosis virus isolated from a parrot in the laboratory of the United States Public Health Service. Yolk sac antigen was prepared by extracting with ether

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4. Bedson, S. P.: The Use of the Complement-Fixation Reaction in the Diagnosis of Psittacosis, Lancet **2**:1277, 1935.

5. Meyer, K. F., and Eddie, B.: The Value of the Complement Fixation Test in the Diagnosis of Psittacosis, J. Infect. Dis. **65**:225, 1939. Smadel, J. E.: Atypical Pneumonia and Psittacosis, J. Clin. Investigation **22**:57, 1943.

6. Rake, G.; Eaton, M. D., and Shaffer, M. F.: Similarities and Possible Relationships Among Viruses of Psittacosis, Meningopneumonitis, and Lymphogranuloma Venereum, Proc. Soc. Exper. Biol. & Med. **48**:528, 1941.

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a 10 per cent saline suspension of heavily infected yolk sacs treated with formaldehyde. The aqueous phase was used as antigen. Allantoic fluid antigen was obtained by cultivating the virus in the allantoic fluid, concentrating the formaldehyde-killed virus ten times by centrifugation and resuspending in 0.85 per cent sodium chloride solution. The technic of fixation was that used by Bengtson[8] for rickettsial antigens, including fixation at 37 C. for one hour. The antigens were of several lots, but all were standardized against a standard pool of serum which gave a positive reaction. Serum samples were tested quantitatively in twofold dilutions, in order to detect the highest dilution in which complete (4 plus) or almost complete (3 plus) fixation occurred in the presence of psittacosis antigen. Samples taken from the same patient at different times were tested together in parallel tests when possible.

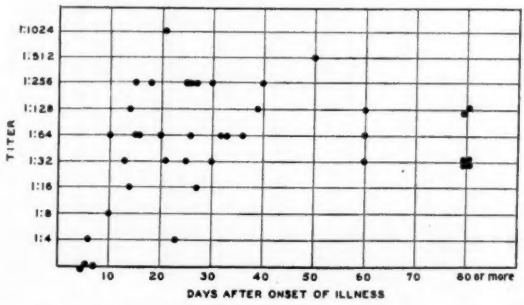

Chart showing complement fixation titers in the serum of 21 patients with psittacosis.

On the basis of significant complement fixation reactions, two groups, totaling 21 cases, were selected from the records of persons whose serum had yielded positive results. These patients presented the clinical features of psittacosis and were reported to have had intimate association with birds. One group was composed of 9 patients whose serum showed a fourfold or greater rise in titer during the course of the illness.[9] The second group was comprised of 12 persons whose serum had a significant titer (1 to 32) when it was first secured ten days, or later, after onset. In order to reduce the chance of including a person previously infected with lymphogranuloma venereum, no person was included for whom a history of venereal disease was obtained or whose serum was known to react positively to tests for syphilis. A summary of the clinical, epi-

8. Bengtson, I. A.: Complement Fixation in the Rickettsial Diseases Technique of the Test, Pub. Health Rep. **59:402, 1944.**

9. The virus was isolated in 1 case.

Case	Patient	Color	Sex	Age (Yr.)	Contact with Birds	Highest Noted Temperature (F.)	Duration of Fever (days)	Principal Signs and Symptoms Reported	Roentgenogram of Chest	Leukocyte Count (per Cu. Mm.)	Complement Fixation Reaction of Serum		Virus Isolation
											Days After Onset	Highest Positive Dilution	
1	R.B.	W	M	55	Kept parakeets; 1 died 1 week prior to onset	102	12	Rales in base of lung, chills, pain in chest, headache, slight cough	Not taken	..	5 13	0 1:32	From patient's sputum on fifth day; unsuccessful on ninth day
2	T.D.A.	W	F	45	2 canaries died	105	60	Consolidation of lung, bradycardia	Pneumonia	10,000 and under	23 32 677	1:4 1:64 1:128	Not attempted
3	S.B.	W	F	53	Patient killed sick English sparrow 2 weeks prior to onset	102.5	6	Rales in base of lungs, pain in chest, chills, sweats, headache	Density at base of left lung and increased hilar shadow		90 days prior to onset 27	0 1:16	Not attempted
4	I.C.	W	F	55	Kept parakeets; none reported sick	104	22	Chills, weakness, anorexia	Peribronchial thickening on fifth day	9,000 8,000	7 21 315	0 1:1024 1:32	From 1 of 2 well parakeets owned by patient
5	?.C.	W	F	47	Pet parakeets (2) died 1 and 3 weeks prior to onset	103	13	Headache	Not taken	6,500	5 14 30	0 1:16 1:32	Not attempted
6	S.S.	W	M	28	Used pigeons as targets in training dogs	105	14	Headache, malaise, sweating	Pneumonitis right hilum	7,000 9,000	10 18	1:8 1:256	Not attempted
7	H.C.	W	M	66	Caught and killed wild pigeons 2 weeks prior to onset	104	19	Headache, malaise, non-productive cough	Reported as normal on thirteenth day of illness	6,300	21 39	1:32 1:128	Not attempted
8	A.W.O.	W	F	..	Parakeets purchased 2 to 3 weeks prior to onset	...	..	Malaise, rales at base of right lung	Infiltration of lower lobe of right lung	..	5–7 14–16 19–21	1:4 1:64 1:64	Not attempted
9	J.W.	W	M	..	Kept pigeons; 1 died prior to onset	103	14	Malaise, anorexia, nonproductive cough; consolidation right lower part of chest	Consolidation middle and lower lobe of right lung	5,000 8,000	4–7 130	1:32 1:228	Not attempted
10	J.C.	C	F	57	Kept parakeets and parrots; none reported sick	104	25	Headache, stiff neck, thoracic pain, slight cough	Reported as normal	..	25 32 36	1:32 1:64 1:64	Not attempted

11	R.K.	W	M	44	Raised pigeons; some were sick	..	21	Malaise, cough, sweats, splenomegaly, rales at base of lungs	Reported as normal	4,800 3,350 3,000 3,750 5,850	26	1:64	Unsuccessful from pigeons
12	C.K.	W	M	38	Raised pigeons; some were sick	...	21	Cough, joint pains, sweats	Thickening of hilar region	6,000	10 26	1:64 1:64	Unsuccessful from pigeons
13	L.P.	W	F	73	2 pet parakeets died 1 week prior to onset	100.4	17	Fever, headache	Not reported	6,500	15	1:64	Not attempted
14	R.P.	W	M	27	Parakeets sold at place of employment; 1 died 3 days prior to onset	104.8	9	Cough, dyspnea, rales throughout chest	Extensive mottling throughout chest	6,100 11,300 9,200	60 230	1:128 1:32	Not attempted
15	A.S.	W	M	..	Pigeons kept near home	103.5	18	Malaise, cough, dull to percussion in right side of chest	Pneumonitis, right side of chest	....	180	1:32	Not attempted
16	C.W.	W	F	35	Pigeons kept at home	104.2	28	Cough, consolidation right upper part of chest, general rales	Consolidation upper lobe of right lung	4,000 4,100	25 40	1:256 1:256	Not attempted
17	B.A.	C	M	43	2 home-bred pigeons died	104.4	17	Minimal consolidation base of lungs, bradycardia, headache, pleuritic pain	Patchy infiltration of lower lobes	5,200 to 9,200	27 50	1:256 1:512	Not attempted
18	F.Z.	W	F	37	Kept pigeons; 2 died 5 days prior to onset	102.8	14	Headache, tachypnea, chills, sweats, rales throughout lungs	Lesion in lower part of right lung	7,750	15 30	1:256 1:256	Not attempted
19	S.A.	W	F	58	1 parakeet died prior to onset	103	..	Malaise, aching, epistaxis	Hilar shadow increased	..	14	1:128	Not attempted
20	C.J.	W	M	40	Kept parakeets; 1 died	...	..	Malaise only reported	Not reported	..	60	1:64	Virus isolated from parakeet
21	—.J.	W	F	38	Kept parakeets; 1 died	..	..	Not reported	Not reported	..	60	1:32	Virus isolated from parakeet

demiologic and serologic data concerning these persons is presented in the table.

All persons herein reported were over 20 years of age, and 13 of the 18 whose exact ages were known were over 40. The group included 11 women and 10 men, and 2 of the 21 were Negro. All of the patients furnished a history of intimate contact with birds: 9 with pigeons (1 of these was with wild pigeons), 9 with parakeets only, 1 with parakeets and parrots, 1 with a feral English sparrow and 1 with canaries. In 16 instances the birds were reported as being sick or dying, and virus was isolated from parakeets belonging to two households involving 3 persons.

Two family outbreaks, involving 2 brothers (cases 11 and 12) and a husband and wife (cases 20 and 21), are included in this series. In each household the onsets were almost simultaneous, suggesting the same source of infection.

The reported principal clinical features consisted of fever, sometimes with temperature as high as 105 F. and lasting usually from one to three weeks, chills, headache, cough, malaise, body ache, sweats and physical signs of pneumonia. Roentgenograms of the chest were reported in 16 cases. In 12 of these there was evidence of pulmonary lesions suggesting pneumonitis, while in 4 cases normal roentgenograms were reported. Leukocyte counts, when performed, were all under 12,000 cells per cubic millimeter. Penicillin was used in some cases and appeared to be of benefit, though the information secured for this group of cases is insufficient to evaluate critically this treatment.

The highest serum dilution fixing complement on the indicated day after onset of the disease is shown in the table. In 15 cases more than one sample was obtained at different times. Demonstrable complement-fixing antibodies usually first made their appearance from the seventh to the tenth day of illness, achieved maximum titer from the twentieth to the thirtieth day and persisted, though in decreased titer, for as long as the serum was tested. In 1 instance, antibodies were present in high titer nearly two years after recovery. Further evidence of the persistence of antibodies is furnished by my experience in 3 cases not included in the table, in which antibodies in low titer were detected four, eight, and sixteen years after the onset of the disease, the diagnosis of which had been originally confirmed in the laboratory of the United States Public Health Service.

The effectiveness of penicillin in the treatment of this frequently fatal disease necessitates a diagnosis as soon as possible and the immediate institution of treatment in persons having psittacosis. The diagnosis may be confirmed by (1) the isolation of the virus from the patient, (2) a fourfold, or greater, rise in complement-fixing antibody titer during the course of illness or (3) a high serum titer after the second week

of illness, together with a history of intimate exposure to birds suspected or known to be infected with psittacosis virus. The cross complement fixation reaction in infections caused by other members of this group of viruses, notably lymphogranuloma venereum, demands care in the interpretation of the results of the test.

SUMMARY

The serum complement fixation reaction, supplemented by clinical and epidemiologic data, furnished the basis for a diagnosis of psittacosis in 21 cases, the disease in none of which was fatal. A fourfold, or greater, rise in antibody titer during the course of illness occurred in the serum of 9 persons, from 1 of whom psittacosis virus was isolated. Serum from 12 persons had a significant titer (1 to 32) when it was first secured ten days, or later, after onset. All persons were reported to have manifested the clinical characteristics of the disease. However, pulmonary lesions were not demonstrated by roentgenograms of the chest in 4 of 16 persons examined. All persons reported intimate contact with birds, chiefly pet parakeets and pigeons. The serum complement fixation reaction became positive about the seventh to the tenth day after onset, achieved maximum titer about the fifteenth to the thirtieth day and persised, though in low titer, for as long as the serum was tested (in 1 instance nearly two years).

PAROXYSMAL COLD HEMOGLOBINURIAS

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DRESSLER[1] is credited with having first reported observations on a case of "paroxysmal cold hemoglobinuria," a symptom complex now known to have two separate and distinct etiologic bases. The first and more generally recognized type is syphilitic paroxysmal cold hemoglobinuria, a disease seen in a small percentage of persons with syphilis and caused by a cold-warm hemolysin unique to persons with syphilis with this disease. The second and nonsyphilitic type is cold hemagglutination paroxysmal hemoglobinuria, a disease accompanied with unusually high titers of cold hemagglutinins and first reported by Salén[2] in 1935 when he recorded observations on pronounced cold agglutination of the red blood cells of a nonsyphilitic patient with paroxysmal cold hemoglobinuria.

This paper will be concerned primarily with the syphilitic type of paroxysmal cold hemoglobinuria. Care was taken to avoid the error of including reports of cold hemagglutination paroxysmal hemoglobinuria in this review of cases of syphilitic paroxysmal cold hemoglobinuria. Only cases reported in sufficient detail regarding clinical and routine laboratory findings have been included.

It is the purpose of this paper to present some observations which were uncovered in this study of 37 case reports of syphilitic paroxysmal cold hemoglobinuria found in the literature since 1930. Points for differentiation between the syphilitic type and the cold hemagglutination type will be given. A new case of syphilitic paroxysmal cold hemoglobinuria treated with penicillin also will be reported, as well as observations on the effect of two of the antihistamine drugs on the cold urticaria that could be produced in this patient.

Circulating in the blood stream of patients with syphilitic paroxysmal cold hemoglobinuria is a hemolysin which, along with complement, is fixed to the red blood cells when the patient is exposed to cold. When the patient subsequently becomes warm, the hemolysin with the aid of complement hemolyzes the red blood cells, releasing hemoglobin into the

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1. Dressler, cited by Macalister[3] and by Mackenzie.[4]

2. Salén, E. B.: Thermostabiles, nicht komplexes (Auto-) Hämolysin bei transitorischer Kältehämoglobinurie, Acta med. Scandinav. **86**:570, 1935.

stream of circulating blood. If the hemoglobinemia exceeds the renal threshold for hemoglobin, the patient will pass cherry red to dark port-wine urine.

With such episodes, the patient experiences a shaking chill often followed by fever and drenching sweats. Generalized abdominal cramps, nausea, generalized weakness, headache and backache are usual, with occasional vomiting. Some form of Raynaud's disease may occur during the paroxysm and urticarious lesions may appear. The paroxysms last for one to two hours, and after them the patient feels well again, except perhaps for some residual weakness and continued vague abdominal distress. The urine remains red or dark for four to ten hours, with urinalysis showing a positive reaction to benzidine, transient albuminuria and occasional red cells and white cells. During or shortly after the paroxysm, the blood shows transient leukopenia, which within a few hours changes to leukocytosis. Repeated attacks leave the patient weak and anemic.

HISTORIC OBSERVATIONS

Macalister[3] in 1908 and Mackenzie[4] in 1929 presented an excellent historical background of this disease. Briefly, according to them, Dressler in 1854 was the first to publish an account of albuminuria with dark red urine in which no red blood cells were to be found. Soon thereafter, Hassall discovered that the pigment was hemoglobin, and he and Gull in 1866 associated the paroxysms with chilling. In 1880, Rosenbach first described the cold water test which bears his name, demonstrating how it was possible to reproduce the acute paroxysm of chills and the dark urine by placing the patient's hands or feet in ice water. Kuessner in 1879 was the first to detect the hemoglobinemia which accompanied the hemoglobinuria. Murri in 1880 called attention to the association of this disease with syphilis, and Ehrlich in 1881 demonstrated that hemolysis occurred locally at the site of chilling.

INCIDENCE

Jones and Jones[5] stated that among 156,000 patients admitted to the Massachusetts General Hospital, Boston, in thirty years there were only 9 cases, and, at Peter Bent Brigham Hospital, Boston, among

3. Macalister, G. H. K.: The Pathology of Paroxysmal Hemoglobinuria: A Critical Review, Quart. J. Med. **2**:368, 1908-1909.

4. Mackenzie, G. M.: Paroxysmal Hemoglobinuria: A Review, Medicine **8**:159 (May) 1929.

5. Jones, B. B., and Jones, C. M.: Paroxysmal Hemoglobinuria, in Nelson Loose-Leaf Living Medicine, New York, Thos. Nelson & Sons, 1920-1929, vol. 4, p. 173A.

74,186 consecutive admissions, there were only 3 cases. Howard, Mills and Townsend[6] found only 2 cases among 208,878 admissions in thirty-eight years at Montreal General Hospital. At the University of Chicago Clinics, there has been only 1 recognized case of syphilitic paroxysmal cold hemoglobinuria in twenty years, during which time approximately 130,000 patients were admitted to the hospital and 382,791 patients were seen in the outpatient clinics.

MECHANICS OF SYPHILITIC PAROXYSMAL COLD HEMOGLOBINURIA, REACTION TO THE DONATH-LANDSTEINER TEST

It was not until 1904 that much was known about the mechanics of this disease. Working independently, Donath and Landsteiner,[7] in Vienna, and Eason,[8] in England, discovered the hemolysin present in the serum of patients with this disease. They demonstrated by in vitro tests that the hemolysin was fixed to the red cells in the cold in the presence of complement and activated to hemolyze the red cells on warming. The Donath-Landsteiner test is the name given today to this reaction. Hemolysis will be seen in a test tube containing the patient's serum, his own cells (or cells of his own type of blood) and complement. Hemolysis will not take place in the control tubes which do not contain complement nor in the tube containing normal human serum. The same hemolysis may also be demonstrated more simply by the Mackenzie rough test, in which the patient's freshly drawn whole blood is allowed to clot, then placed in ice water for ten minutes, followed by warming at 37 C. (198.6 F.) for one-half hour.

This hemolysin, the presence of which can be detected by the Donath-Landsteiner or Mackenzie rough tests, is known as the cold-warm hemolysin. It has not been demonstrated in consistent association with any disease other than syphilis. The observation of a positive reaction to the Donath-Landsteiner test in a patient with a history of paroxysms of chills and dark urine following exposure to cold can be considered pathognomonic of syphilitic paroxysmal cold hemoglobinuria.

It is important to remember that in a true, positive reaction to the Donath-Landsteiner test for syphilitic paroxysmal cold hemoglobinuria, hemolysis occurs only after the mixture of serum, cells and complement has been warmed, not before. As early as 1913, Widal, Abrami and

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6. Howard, C. P.; Mills, F. S., and Townsend, S. R.: Paroxysmal Hemoglobinuria with Report of Case, Am. J. M. Sc. **196**:772 (Dec.) 1938.

7. Donath, J., and Landsteiner, K.: Ueber paroxysmale Hämoglobinurie, München. med. Wchnschr. **51**:1509, 1904.

8. Eason, J.: The Pathology of Paroxysmal Hæmoglobinuria, J. Path. & Bact. **11**:167, 1906.

Brissaud[9] stressed the importance of keeping the blood at a temperature of 37 C. from the time it is drawn from the patient to the time it is chilled. Blood from nonsyphilitic patients with paroxysmal cold hemoglobinuria due to high titer of cold hemagglutinins (cold hemagglutination paroxysmal hemoglobinuria) will hemolyze on exposure to cold alone without rewarming. This possible source of error in interpretation of the Donath-Landsteiner test may be responsible for some of the confusion existing in the literature concerning reports[10] of "paroxysmal cold hemoglobinuria" with a "positive" reaction to the Donath-Landsteiner test and a negative reaction to the Wassermann test.

York and Macfie[11] in 1921 showed that in the reaction to the Donath-Landsteiner test the hemolysis decreased in direct proportion to the increase in time of exposure to cold beyond seven minutes. By the end of twelve to fifteen hours, no hemolysis could be expected. Their theories concerning this behavior of the hemolysin on prolonged exposure to cold centered about depletion of available complement.

Burmeister[12] in 1921 concluded from his work that the hemolysin could not be distinguished or separated from the Wassermann reagin. Subsequent workers, including Smith[13] in 1923, Puris[14] and Mackenzie[4] in 1929 and others, consistently observed that the hemolysin is an entity distinct and separate from the reagin. This distinction can easily be

9. Widal, F.; Abrami, P., and Brissaud, E.: Recherches sur l'hémoglobinurie paroxystique à frigore, Compt. rend. Soc. de biol. **65**:429, 1913.

10. (*a*) Donath, J., and Landsteiner, K.: Ueber Kältehämoglobinurie, Ergebn. d. Hyg., Bakt. **7**:184, 1925. (*b*) Ernstene, A. C., and Gardner, W. J.: The Effect of Splanchnic Nerve Resection and Sympathetic Ganglionectomy in a Case of Paroxysmal Hemoglobinuria, J. Clin. Investigation **14**:799 (Nov.) 1935. These authors observed pronounced agglutination of their patient's red blood cells when specimens of his freshly drawn blood were exposed to room temperature, an observation which clearly puts this case in the cold hemagglutination type of "paroxysmal cold hemoglobinuria." (*c*) Roch, M. M., and Liengme, A.: Hémoglobinurie paroxystique et angine éryhthémateuse "a frigore," Bull. et mém. Soc. méd. d. hôp. de Paris **46**:1737, 1922. (*d*) Lopes, D. M.: Hemoglobinuria paroxistica "a frigore," Brasil-med. **48**:486 (Dec. 16-30) 1944. The author reported that in addition to obtaining a "positive" reaction to the Donath-Landsteiner test and a negative reaction of the blood to the Kahn test, he was unable to make a red blood cell count for his patient because of the extreme agglutination of the cells.

11. York, W., and Macfie, J. W. S.: Mechanism of Autolysis in Paroxysmal Hemoglobinuria, Brit. J. Exper. Path. **2**:115 (June) 1921.

12. Burmeister, J.: Ueber paroxysmale Hämoglubinurie and Syphilis, Ztschr. f. klin. Med. **92**:19, 1921.

13. Smith, R. P.: The Relationship of the Autolysin and the Wassermann Antibody in the Serum of a Paroxysmal Hemoglobinuria, J. Path. & Bact. **26**:196, 1923.

14. Puris, A. M.: Paroxysmal Hemoglobinuria, Am. J. Dis. Child. **37**:1027 (May) 1929.

demonstrated by absorbing the hemolysin on red blood cells in the cold and quickly separating the serum. This absorbed serum will no longer hemolyze the patient's red blood cells but will still give a Wassermann reaction as strongly positive as before absorption. Maire[15] in 1945 discussed the transient effect of alkalis in decreasing hemolysis and hemoglobinuria.

The cold urticaria frequently seen in patients with syphilitic paroxysmal cold hemoglobinuria during an acute paroxysm is due to the action of a substance in their serum called dermolysin. This dermolysin injures the cells of the skin on exposure to cold followed by warming much the same as the hemolysin lyses the red blood cells; it is probably the same substance as the hemolysin.[16]

Corroborative clinical and laboratory evidence can be gained from the cold water (Rosenbach) test in which the patient's hands or feet or both are placed in ice water from fifteen to thirty minutes. After becoming warm, the patient with this disease may experience an acute paroxysm exhibiting the characteristic clinical features, including the passage of cherry red to dark urine. It has been suggested that in performing the cold water test for the first time on a patient, caution should be observed and only the hands immersed in ice water. This word of warning is well taken, for Stevenson[17] in 1943 reported on a patient with syphilitic paroxysmal cold hemoglobinuria who was anuric for two days after a cold water test with both his hands and feet immersed for one-half hour.

As was pointed out by York and Macfie,[11] repeated cold water tests may deplete the complement to such a point that a reaction may no longer be detected. It was observed of the present patient with syphilitic paroxysmal cold hemoglobinuria that his clinical reactions and the degree of hemoglobinuria following the cold water test varied from day to day. In the evaluation of any form of therapy by means of the patient's reactions to cold water tests, these variations and fluctuations should be kept in mind.

REPORT OF A CASE OF SYPHILITIC PAROXYSMAL COLD HEMOGLOBINURIA

F., 56 years of age, white male maintenance worker, was first seen at the Albert Merritt Billings Hospital, of the University of Chicago, on May 18, 1946, with the

15. Maire, E. D.: Paroxysmal Hemoglobinuria Due to the Cold Hemolysin: Observations with a Report of a Case of Its Occurrence in an Aerial Gunner, Arch. Int. Med. **76**:292 (Nov.-Dec.) 1945.

16. Harris, K. E.; Lewis, T., and Vaughan, J. M.: Haemoglobinuria and Urticaria from Cold Occurring Singly or in Combination: Observations Referring Especially to Mechanism of Urticaria with Some Remarks upon Raynaud's Disease, Heart **14**:305 (March) 1929.

17. Stevenson, I. P.: Paroxysmal Hemoglobinuria with Report of a Case, McGill M. J. **12**:192 (Oct.) 1943.

complaint of abdominal pain, a loss in weight of 15 pounds (6.8 Kg.) and constipation for one year. The abdominal pain was vague, dull and aching in character and generalized over the mid and lower portions of the abdomen; it was not associated with meals or emotional stress, nor was it relieved by anything specific. He had noted some increased fatigability and a loss in weight of 15 pounds in the past year, though his appetite was still good. One month before his admission, he stated he passed bloody urine, with chills, sweating, tingling in hands and feet, malaise and weakness which came on after he was outdoors on a cold, damp day. This was the first time he had ever been aware of such an attack. There was no history of cold urticaria or cyanosis.

The family history gave no suggestion of syphilis. The past history[18] revealed that the patient had gonorrhea at 19 years of age, but no history of chancre, rash or other signs of acquired syphilis was obtained.

Physical examination revealed the blood pressure to be 140 systolic and 80 diastolic. The temperature was 37 C. (98.6 F.); pulse rate was 96 and regular, and the respirations numbered 18 per minute. The patient appeared chronically ill. The skin was clear. The pupils were regular and equal and reacted to light and accommodation. In the left lobe of the thyroid gland was a stony hard nodule the size of a walnut. The remainder of the gland was moderately enlarged, and no bruit was heard. The lungs were clear; the heart was normal. A few, small, subcutaneous lipomas were felt over the abdominal wall; no organs or other masses were palpable. Genitourinary organs were normal. The extremities showed no edema or gangrene. Reflexes were equal and active. There were coarse and fine tremors of the head and extended hands; the gait was normal.

Laboratory studies of the blood revealed 3,790,000 red blood cells per cubic millimeter, 12 Gm. hemoglobin per hundred cubic centimeters and 9,000 white blood cells, with 60 per cent polymorphonuclear leukocytes, 24 per cent lymphocytes, 13 per cent monocytes and 3 per cent eosinophils. Urinalysis revealed 3 to 4 white blood cells per high power field, a trace of albumin and no red blood cells.

The blood type was ORh negative. Red blood cells showed normal fragility. The blood was negative for cold isoagglutinins. Sternal puncture showed moderate hyperplasia of the normoblastic series. Gastric analysis revealed the presence of free acid after administration of histamine. The stools showed no occult blood with the patient on a diet free from meat. Nonprotein nitrogen measured 27 mg.; plasma proteins totaled 7.82 Gm., with 4.21 Gm. albumin and 3.61 Gm. globulin, per hundred cubic centimeters. Serum cholesterol totaled 240 mg., with 173 mg. cholesterol esters per hundred cubic centimeters. Basal metabolism rate on June 11 was +20 per cent and on June 29 +34 per cent. On June 30 administration of strong iodine solution U.S.P., 10 drops three times a day, was started. On July 6 the rate was +6 per cent; on July 19 subtotal thyroidectomy was performed, with the pathologic diagnosis of adenomatous goiter with calcified shell of left lobe and hyperplasia of isthmus. On August 3, basal metabolic rate was —18 per cent.

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18. Dickson, J. G.: Paroxysmal Hemoglobinuria with Report of Case Followed for Thirteen Years, U. S. Nav. M. Bull. **34**:300 (July) 1936. This report of syphilitic paroxysmal cold hemoglobinuria is demonstrative of the well recognized difficulty of obtaining a positive history of syphilis. Though the patient, a 40-year-old man, repeatedly denied any history of chancre, rash or antisyphilitic therapy, a check on his Naval hospital record showed that while in the United States Navy twenty-one years before he had been admitted to sick bay with a secondary syphilitic eruption and had received antisyphilitic therapy.

Roentgenographic examinations of esophagus, stomach, duodenum, terminal part of the ileum and the colon showed them to be normal. Intravenous pyelogram revealed nothing abnormal. Roentgenogram of the chest showed pulmonary fields to be clear, with calcification in the left lobe of the thyroid gland.

On the electrocardiogram the QRS complex was broad and slurred and at the lower limits of normal amplitude in the leads on the limbs. The T-Cf wave was at the upper limit of normal.

Five serologic determinations were made between May 18 and September 8; reactions to the Wassermann and the Kahn tests were strongly positive (4 plus for each test).

Cerebrospinal fluid was obtained under normal pressure. No cells were seen on examination. To the Wassermann and Kahn tests reactions were negative, and protein measured 38 mg. per hundred cubic centimeters. The results of the colloidal gold curve test were normal.

The Donath-Landsteiner tests received repeatedly positive reactions at serum dilutions of 1:1 and 1:2. The reactions to the Mackenzie rough tests were repeatedly strongly positive. For the first cold water test, the patient's hands were allowed to remain in ice water for ten minutes. No reaction occurred, and the urine remained light and clear. On the second test the hands and feet were placed in ice water twenty minutes. The reaction was positive, with a shaking chill followed by elevation in temperature up to 101 F., cyanosis of lips and ear lobes, blanching of finger tips and fingers, headache, nausea and generalized abdominal distress. Forty-five minutes after removal of hands and feet from ice water, the patient passed cherry red urine with a strongly positive benzidine reaction, showing 0 to 2 red blood cells and 5 to 10 white blood cells per high power field and a 1 plus reaction for albumin in a centrifuged specimen. The patient felt perfectly well two hours after completion of the test, but hemoglobinuria persisted for eight hours. Electrocardiograms taken during and two hours after the paroxysm showed no change from that made on his admission to the hospital. The white blood cell count rose from 8,800 to 13,000 four hours after conclusion of the paroxysm from the cold water test. An ice water enema retained for three minutes produced severe abdominal cramps, no hemoglobinemia and no hemoglobinuria.

Special laboratory work gave the following results:

Serum from which the hemolysin had been absorbed by exposure of 10 cc. of the patient's whole blood to 0 C. (32 F.) for seven minutes gave strong 4 plus Wassermann and Kahn reactions but negative cutaneous reactions to tests for the dermolysin. No hemolysin was demonstrable in cerebrospinal fluid. Just as much hemolysis was detectable grossly when the patient's whole blood was exposed to 0 C. for one minute (followed by one-half hour at 37 C.) as when it was exposed to 0 C. for seven minutes and thirty minutes, slightly less hemolysis when exposed for sixty minutes, appreciably less at three hours, faint hemolysis at eight hours and no hemolysis after his whole blood was exposed to 0 C. for twelve hours followed by exposure at 37 C. for one-half hour (supporting evidence for the results and concept of York and Macfie[11]).

Chilling of freshly drawn whole blood at 20 C. (68 F.) began fixation of complement and hemolysin to red blood cells, which was complete at 15 C. (59 F.); no hemolysis was observed when the blood was chilled to only 25 C. (77 F.), followed by exposure to 37 C. for one-half hour. Consistently greater hemolysis was noted when the patient's serum was used with cells of normal persons in the same blood group (0) than when the patient's own cells were used. When cells of the other blood groups were used, no hemolysis or only slight hemolysis was detected;

no more was seen than one would expect from the combined agglutination and hemolytic reaction of incompatible serums and cells.

REVIEW OF CASE REPORTS PUBLISHED SINCE 1930

The literature was surveyed back to and including 1930 for reports of cases of syphilitic paroxysmal cold hemoglobinuria sufficiently detailed to include a history and results of physical examination, the Donath-Landsteiner test, serologic tests for syphilis and routine laboratory work. Thirty-seven such case reports were available in the literature. Many of the reports appeared in foreign journals, a few of which were not obtainable owing to the recent international crisis. The pertinent information found in these 37 reports is summarized in table 1 and analyzed in table 2, which is self explanatory. These tables will be referred to in the subsequent discussion on etiology and immunity. Included in the interpretive review is the present case report of patient F.

ETIOLOGIC ASPECTS AND THE ROLE OF SYPHILIS

Murri[19] in 1885 was the first to point out a relation between cold hemoglobinuria and syphilis. Since that time, almost all students of this disease have upheld his conclusion and have emphasized the role of syphilis in the etiology of cold hemoglobinuria due to the cold-warm hemolysin. Despite the unanimity of opinion prevailing in the literature, some doubt still remains as to the syphilitic nature of this disease, and some consideration is still given to the notion that the positive serologic reactions seen in these patients are false positive reactions. This consideration is no longer justified. Probably the one factor most responsible for the unwillingness of some workers to accept the syphilitic basis for this disease is the customary absence of clinical manifestations of active syphilis. This apparently paradoxic situation could be interpreted in terms of immunity, as will be discussed later, and it should not be held up as evidence against a syphilitic origin.

The records of children with hemoglobinuria due to the cold-warm hemolysin strongly indicate that patients with this disease have at some time in the past been infected by the spirochete of syphilis. A child more than 6 months of age with persistent positive serologic reactions whose mother's reactions are also positive must be considered a syphilitic child, in spite of lack of clinical evidence of congenital syphilis.

Of the 37 case reports reviewed for this paper, 10 were of children, and all 10 children were more than 6 months of age. In 8 of these 10 cases the parents were investigated, and in each of the 8 cases a positive family incidence of syphilis was established by history, serologic reac-

19. Murri, A., cited by Mackenzie.[4]

TABLE 1.—*Reports of 37 Cases of Syphilitic Paroxysmal Cold Hemoglobinuria Found in the Literature Since 1930, with Report of Present Case*

Author and Reference	Age, Yr., and Sex	Serologic Reaction	History of Syphilis, Acquired or Congenital	Clinical Evidence of Active Syphilis Other Than Serologic Reactions and Cold-Warm Hemolysin*	Results of Antisyphilitic Therapy
Inamori, S.: Am. J. Dis. Child. 44:379 (Aug.) 1932	7 M	++++Wassermann	Not given	None	Cured by fever therapy with Spirillum minus (and 5 injections neoarsphenamine U. S. P.)
Ito, N.: Am. J. Dis. Child. 46:1062 (Nov.) 1933	4 F	++++Wassermann	Not given	None	Cured by fever therapy with Spirillum minus (and 5 injections neoarsphenamine)
Pilot, I., and Friedman, H.: M. Clin. North America 13:1231 (March) 1930	49 M	Strongly positive Wassermann and Kahn	Negative	None	Disappearance of hemoglobinuria but Wassermann and Kahn reactions still strongly positive
Hughes, J. F.: M. J. Australia 2:503 (Dec. 18) 1943	22 M	Strongly positive	Negative	None	Not mentioned
Stevenson (Footnote 17)	43 M	Positive	Negative	None	Not mentioned
Woofter and Parks (Footnote 24)	30 M	++++Wassermann, ++++Kahn	+Wassermann reaction 9 yr. before, treated with arsenicals	None Negative cerebrospinal fluid reaction	Disappearance of hemoglobinuria but appearance of tabetic form of dementia paralytica with positive cerebrospinal fluid reaction 1 yr. later
Maire (Footnote 15)	26 M	Positive	Negative	None	Disappearance of hemoglobinuria; Donath-Landsteiner reacton reversed to negative
Goldberg (Footnote 31)	26 M	Strongly positive	Negative	None	Ameliorated: treatment with 3,000,000 units pencillin; still had hemoglobinuria on exposure to cold but paroxysms appeared less severe
Jedlicka, V., and Kral, J.: Sang 5:654, 1931	19 M	Positive	Positive	None	Hemoglobinuria ameliorated
	28 M	Positive	Negative	None	Clinical cure
Huang, C. H., and Sia, R.H.P.: Chinese M. J. 50:214 (March) 1936	39 M	Strongly positive	Multiple venereal contact	None	Clinical cure
Jaffe, L.: J. Michigan M. Soc. 34:312 (May) 1935	47 M	++++Wassermann	Gonorrhea at age 16; syphilis denied	None	Ameliorated
Bojlen, K.: Acta paediat. (supp. 1) 17:324, 1935	5 M	Strongly positive	Both parents: positive Wassermann reactions	None	Not mentioned
	11 F	Positive	Mother: +++Kahn	None	Not mentioned

Phillips, J. T., Jr., and Hogg, P.: Virginia M. Monthly 66:737 (Dec.) 1939	4 M	++++Wassermann ++++Kahn	Mother: ++++Wassermann	None	Not mentioned
Logue, R. G.: J.M.A. Georgia 30:275 (June) 1941	13 M	++++Wassermann ++++Kahn	Mother had syphilis	None	Ameliorated
Mitacek, S.: Sang 6:153, 1932	35 M	Positive	Syphilis for 13 yr.	None	Not mentioned
Kelly, H. T.: Pennsylvania M. J. 37:393 (Feb.) 1934	33 F	Wassermann negative	Negative	None	Satisfactory
	10 F	Strongly positive	Mother had syphilis	None	Satisfactory
Rosen, S. F.: South. M. J. 26:1038 (Dec.) 1933	36 M	++++Kahn Wassermann (anticomplementary)	Chancre 8 yr. before	None	Not mentioned
Swineford, O., Jr.: J. Lab. & Clin. Med. 16:347 (Jan.) 1931	30 M	Strongly positive	Wife has syphilis; patient had penile sore	None	Ameliorated
Agnoli, R.: Minerva med. 2:731 (Nov.) 1932	34 F	Strongly positive	Positive with secondary syphilis	None	Not mentioned
Cattaneo, L.: Gior. ital. di dermat. e sif. 72:1159 (Oct.) 1931	33 M	Very strongly positive	Positive with chancre	None	Ameliorated
Purig, Leal, J.: Arch. de med., cir. y especialid. 35:113 (Feb. 6) 1932	32 M	Positive	Positive with chancre	None	Not mentioned
Dickson (Footnote 18)	40 M	Strongly positive	Secondary syphilis with mucous patches 21 yr. before	None	Disappearance of hemoglobinuria after therapy with mercury succinimide and neoarsphenamine; clinical cure followed 13 years
Howard and associates (Footnote 6)	33 M	Strongly positive	Gonorrhea 10 yr. before; syphilis denied	None	No hemoglobinuria after 3 mo. antisyphilitic therapy; followed 1 yr.
Thurmon and Blaine (Footnote 23)	23 F	Positive Wassermann; positive Kahn; positive Hinton	Mother had + Wassermann reaction	None	Not given
	20 M	Positive Wassermann; positive Hinton	Negative	None	Hemoglobinuria ameliorated
	46 F	Positive Wassermann	Patient and husband had chancre	None	Hemoglobinuria disappeared; later active syphilis set in, with perforated septum and tabes; no recurrence of hemoglobinuria
d'Alessandro, G.: Riforma med. 51:1280 (Aug. 24) 1935	44 M	++Kahn	History of chancre	None	Not mentioned
Wassmann, K.: Ugesk. f. laeger 99:771 (July 15) 1937	3 F	Very strongly positive	Mothers serologic reaction strongly positive	None	Not mentioned

TABLE 1.—*Reports of 37 Cases of Syphilitic Paroxysmal Cold Hemoglobinuria Found in the Literature Since 1930, with Report of Present Case—Continued*

Author and Reference	Age, Yr., and Sex	Serologic Reaction	History of Syphilis, Acquired or Congenital	Clinical Evidence of Active Syphilis Other Than Serologic Reactions and Cold-Warm Hemolysin*	Results of Antisyphilitic Therapy
Moorman, E. R.: Virginia M. Monthly 61:14 (April) 1934	38 M	++++Wassermann	Chancre 15 yr. before	None	Clinical cure of hemoglobinuria but Wassermann reaction still ++++
Hall, S. C., Jr., and Barksdale, E. E.: Virginia M. Monthly 65:126 (March) 1938	9 M	+Wassermann, +++Kahn	Father; + Wassermann	None	Clinical cure
Lewis, S. J., and Fears, T. A.: Texas State J. Med. 32:403 (Oct.) 1936	31 F	Strongly ++++Wassermann and Kahn reactions	Negative	None	Ameliorated
Brule, M.; Hillemand, P., and Gaube, R.: Bull. et mem. Soc. med. d. hop. de Paris 53:197 (Feb. 22) 1937	55 M	Strongly positive	Negative	None	Not mentioned
McCarthy and Wilson (Footnote 21)	23 M	Strongly positive Wassermann and Kahn reactions	Chancre at 17 yr. of age	None	Disappearance of hemoglobinuria
	5 F	Positive	Mother had positive Wassermann reaction	Interstitial keratitis	Disappearance of hemoglobinuria
F. (present case)	56 M	Very strongly ++++Wassermann, ++++Kahn	Denied	None	Clinical cure with 5,000,000 units of penicillin but still has occasional moderately positive in vivo and in vitro tests and strongly positive serologic reactions

*"Clinical evidence of active syphilis" means clinical manifestations of invasive spirochetal activity, excluding lesions such as Hutchinson teeth and rhagades which are not active foci but old scars and degenerative residua.

tions or clinical evidence of the latent or manifest forms in parents or siblings.

There is no reason to consider that, while the positive serologic reactions in children with this disease are then admittedly true positive reactions, the positive serologic reactions in the adults are false positive the two age groups are identical symptomatically and clinically. No variation has ever been described between the nature of the cold-warm hemolysin of the child and the nature of that of the adult, or in its mechanism as studied in vitro.

TABLE 2.—*Analysis of Reports of 38 Cases of Syphilitic Paroxysmal Cold Hemoglobinuria Appearing in the Literature Since 1930 (Including Present Case).*

History of Syphilis—Familial or Acquired	
Negative	13
Positive	23
Clinical Evidence of Active Syphilis (Besides Serologic Reaction and Cold-Warm Hemolysin)	
Not mentioned	2
Present	0
Absent	38
Serologic Reactions	
"++++," "strongly positive" or "very strongly positive"	24
"Positive"	11
Doubtful, +1, ++ or +++	2
"Negative"	1
Results of Antisyphilitic Treatment	
Clinical "cure"	15
Cold hemoglobinuria ameliorated	10
No success with apparently adequate treatment	0
Not mentioned	13

Another strong argument in favor of the syphilitic origin of the cold-warm hemolysin is the good response to adequate antisyphilitic therapy that can be expected in the majority of these patients, children or adults.

New and interesting evidence again implicating syphilis in the etiology of this disease comes from Neurath,[20] who recently worked out a technic for better differentiation between false positive and true positive serologic reactions for syphilis. Neurath observed that the serum of patient F. gave a true syphilitic type reaction. In addition, the Wassermann and Kahn reactions of this patient have remained strongly positive for two years, consistent with a true syphilitic reaction.

As shown in table 2, clinical evidence of invasive spirochetal activity was absent in each of the 38 patients with syphilitic paroxysmal cold hemoglobinuria.[21] Without the cold hemoglobinuria, these patients

20. Neurath, H.: False Positive Reactions in the Serology of Syphilis, J. Ven. Dis. Inform., 1945, supp. 20, p. 134.

would be considered to be in the latent stage of late seropositive syphilis, congenital or acquired. Consideration might also be given to the concept that syphilitic paroxysmal cold hemoglobinuria represents an immune state in syphilis, possibly of an unusual nature. However, the presence of the cold-warm hemolysin in the blood of 20 per cent of persons with late and latent syphilis, as observed by Kumagai and Jnoue,[22] in the absence of hemoglobinuria indicates that the basic mechanism producing the hemolysin is not unusual. That it was proved absent by these same workers in all 13 patients with secondary syphilis studied by them further points to the presence of the hemolysin only in the presence of immunity as it develops in the late stages. Jones and Jones[5] reported a positive reaction to Donath-Landsteiner test in 6.6 per cent of 45 persons with syphilis they studied. They did not mention the clinical phases of syphilis represented in their patients. Perhaps the degree of hemolysin titer parallels the degree of immunity. Syphilitic persons with hemoglobinuria have a high titer of the cold-warm hemolysin and do not present clinical manifestations of an active syphilitic infection.

Reports of cases by Thurmon and Blaine[23] and Woofter and Parks[24] are of considerable interest in such speculation. In 1931 Thurmon and Blaine reported on 3 patients with syphilitic paroxysmal cold hemoglobinuria, 1 of whom was a 46 year old woman. She and her husband had a history of chancre. On admission of the wife to the hospital on Nov. 7, 1917, examination revealed cold hemoglobinuria with positive reactions to Donath-Landsteiner tests and a positive reaction to the Wassermann test, with no other evidence of syphilis. During this stay in the hospital she received antisyphilitic therapy in the form of potassium iodide orally, mercury succinimide intramuscularly and two intravenous injections of arsphenamine U.S.P. ("diarsenol"). She was readmitted two days after her discharge, on December 20, with acute exacerbation of her cold hemoglobinuria; she received five more injections of mercury succinimide and was discharged about two weeks later. She was not seen for almost seven years, during which time she had no

21. McCarthy, F. P., and Wilson, R., Jr.: Paroxysmal Hemoglobinuria: Report of Cases, with Familial Findings, New England J. Med. **207:** 1019 (Dec. 8) 1932. This case of interstitial keratitis was in a 5 year old girl who had paroxysms of cold hemoglobinuria. However, interstitial keratitis is itself an indirect result of congenital syphilis of nutritional, degenerative or allergic nature and is not caused by direct invasion of the cornea by spirochetes.

22. Kumagai, T., and Jnoue, B.: Beiträge zur Kenntnis der paroxysmalen Hämoglobinurie, Deutsche med. Wchnschr. **38:**361, 1912.

23. Thurmon, F., and Blaine, D.: Paroyxsmal Hemoglobinuria: Observation Based upon Study of Three Cases, Am. J. Syph. **15:**350 (July) 1931.

24. Woofter, A. C., and Parks, B. S.: Paroxysmal Hemoglobinuria with Report of Case, Ann. Int. Med. **12:**402 (Sept.) 1938.

further recurrence of her cold hemoglobinuria, though she was frequently exposed to the cold. On Nov. 24, 1924, she was readmitted with dyspnea, absent ankle jerks, perforated septum and positive reaction to the Wassermann test, but she had no recurrence of her cold hemoglobinuria. Seven years later, on May 12, 1931, she still had a positive reaction to the Wassermann test but no cold hemoglobinuria.

Woofter and Parks[24] in 1938 reported on a patient with syphilitic cold hemoglobinuria, with positive reactions to Wassermann, Donath-Landsteiner and Rosenbach cold water tests. No other clinical evidence of syphilis was present. Antisyphilitic therapy was started, and thereafter the patient had no recurrence of his cold hemoglobinuria. However, about one year later, while the patient was receiving antisyphilitic therapy and still had positive serologic reactions, mental dulness, apathy and uneven gait developed, with diagnosis of the tabetic form of dementia paralytica, but he had no recurrence of his cold hemoglobinuria.

Apparently, in these cases the treatment was enough to upset the immune balance and depress the hemolysin but was inadequate to rid the tissues of the spirochete. With the "natural" immune state upset, important defenses of the body against further invasion by the spirochete were removed.

No cases of hemoglobinuria or of positive reactions to the Donath-Landsteiner tests in the parents of persons with congenital syphilitic hemoglobinuria are reported. Thus, there is no reason to assume that formation is the result of infection by a specific strain of Treponema pallidum.

SYPHILITIC PAROXYSMAL COLD HEMOGLOBINURIA AND COLD HEMAGGLUTINATION PAROXYSMAL HEMOGLOBINURIA

It has become increasingly evident in recent years that the diagnosis "paroxysmal cold hemoglobinuria" is inadequate. Two spearate and distinct disease processes capable of producing intravascular hemolysis on exposure to cold are now recognized. One is syphilitic paroxysmal cold hemoglobinuria due to a cold-warm hemolysin. The other is cold hemagglutination paroxysmal hemoglobinuria due to an abnormally high titer of cold hemagglutinins. In the breakdown of red cells due to high titers of cold hemagglutinins, no hemolysin has been demonstrated. Since Salén's description of this later condition in 1935, more and more reports of cases are appearing.[25] As early as 1909, Moro, Noda and

25. Ernstene and Gardner,[10b] Lopes,[10d] McCombs, R. P., and McElroy, J. S.: Reversible Auto-Hemagglutination with Peripheral Vascular Symptoms, Arch. Int. Med. **59**:107 (Jan.) 1937. Roth, G.: Paroxysmal Hemoglobinuria with Vasomotor and Agglutinative Features, Proc. Staff Meet., Mayo Clin. **10**:609 (Sept. 25) 1935. Stats, D., and Bullowa, J. G. M.: Cold Hemagglutination with Symmetric Gangrene of the Tips of the Extremities: Report of Case, Arch. Int. Med. **72**:506 (Oct.) 1943.

Benjamin[26] pointed out that those cold hemoglobinurias which occur in a person with a negative reaction to the Wassermann test belong in some other category, because they are not caused from syphilis.

Stats[27] made clear that four points must be fulfilled to demonstrate in vitro the breakdown of red cells due to a high titer of cold hemagglutinins: (1) the presence in high titer (over 1:3,000) of the cold hemagglutinin, (2) a cold-maintained environment, (3) slight agitation of the mixture of red cells and serum paralleling the trauma to which the red cells are subject in the stream of circulating blood and (4) a sufficient volume of red cells on which the cold hemagglutinin may act.

The following points of differentiation between syphilitic paroxysmal cold hemoglobinuria and cold hemagglutination paroxysmal hemoglobinuria may be summarized:

1. Cold agglutinins are absent in the syphilitic type but present in high titer (over 1:3,000) in the cold hemagglutination type. They can usually be detected by a routine red blood cell count at room temperature.

2. In the syphilitic type, the reactions to the Donath-Landsteiner or Mackenzie tests are positive; in the cold hemagglutination type, they are negative, that is, hemolysis takes place without warming or no hemolysis occurs.

3. In the syphilitic type, a positive reaction of the blood to Wassermann and Kahn tests can be considered essential for the diagnosis; in the cold hemagglutination type, a positive reaction to Wassermann or Kahn tests is practically never present, and if such a reaction is present in the absence of a positive reaction to Donath-Landsteiner, it can be considered coincidental.

4. In the syphilitic type, complement is required. Wintrobe,[28] in speaking of simply "paroxysmal cold hemoglobinuria," cited the reports of Ernstene and Gardner[10b] and Salén[2] as descriptions of cases not requiring complement. Both these cases were of cold hemagglutination paroxysmal hemoglobinuria, the authors observing conspicuous agglutination of red cells in routine examinations of the blood of their patients. Both these patients also had negative serologic reactions. Complement is not required in the cold hemagglutination type.

5. In the syphilitic type, a dermolysin can practically always be demonstrated. (Harris and associates[16] reported 1 case of syphilitic

26. Moro, E.; Noda, S., and Benjamin, E.: Paroxysmale Hämoglobinurie und Hämolyse in Vitro, München. med. Wchnschr. **56**:545, 1909.

27. Stats, D.: Cold Hemagglutination and Cold Hemolysis: Hemolysis Produced by Shaking Cold Agglutinated Erythrocytes, J. Clin. Investigation **24**:33 (Jan.) 1945; Cold Agglutinated Erythrocytes: Hemolytic Effect of Shaking, Proc. Soc. Exper. Biol. & Med. **54**:305 (Dec.) 1943.

28. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1942, pp. 429-430.

paroxysmal cold hemoglobinuria with no demonstrable dermolysin.) No reports were found of a dermolysin demonstrable in the serum of patients with the cold hemagglutination type.

6. Cold urticaria is frequently seen during the paroxysms in the syphilitic type. Stats and Wassermann[29] reported no authentic cases on record of cold urticaria associated directly with the paroxysm in the cold hemagglutination type.

7. In the syphilitic type the hemolysin is type specific, while the cold hemagglutinin will act on blood of other types, as well as on the blood of other animals (Stats and Wassermann[29]).

It is interesting that of the 2 cases of "paroxysmal cold hemoglobinuria" on record at the University of Chicago Clinics, 1 of them (the present case) was of the syphilitic type, while the other was of the type due to high titer of cold hemagglutinins. The patient with the latter type experienced severe hemolytic crises with paroxysms of hemoglobinuria after exposure to cold and had eight admissions to the hospital for transfusions. The red blood cells of this patient agglutinated so strongly at room temperatures that it was difficult to count the red cells without warming each bit of equipment with which they came in contact. When needles, syringes and test tubes were warmed, it was seen that the patient's blood was not hemolyzed if chilled without agitation then warmed (negative reaction to Donath-Landsteiner and Mackenzie tests). This patient also had repeated negative blood Wassermann and Kahn reactions. With his attacks and between attacks he experienced the same vague abdominal distress with anorexia, nausea and vomiting as experienced by patient F., who had syphilitic paroxysmal cold hemoglobinuria.

Treatment of cold hemagglutination paroxysmal hemoglobinuria is uncertain and unsatisfactory. As one would expect there are no reports of success with antisyphilitic therapy. Ernstene and Gardner[10b] in 1935 reported satisfactory amelioration with sympathectomy in their patient.

ANTIHISTAMINE DRUGS AND THE DERMOLYSIN

In many patients with syphilitic paroxysmal cold hemoglobinuria cold urticaria develops, along with the attacks of chills and dark urine, on exposure to cold. Harris, Lewis and Vaughan[16] comprehensively covered this aspect of syphilitic paroxysmal cold hemoglobinuria, concluding that the dermolysin causing the urticaria is either the same substance as the hemolysin or a closely allied substance. The antibody which causes cold urticaria in these patients can be transferred passively to nonsensitive persons. If serum of the patient is injected intradermally

29. Stats, D., and Wassermann, L. R.: Cold Hemagglutination—An Interpretive Review, Medicine **22**:363 (Dec.) 1943.

into a nonsensitive test subject and the injection site is chilled and warmed, an erythematous, pruritic wheal appears. This was demonstrated in the case of patient F. However, it was observed, that, if the hemolysin was absorbed from his serum by exposure of a tube of his whole clotted blood to the cold followed by quick centrifiugation in ice-packed tubes, the dermolysin was also absorbed and no wheal could be produced by intradermal administration (and cold-warm treatment) of this absorbed serum either by injection into patient F. or by passive transfer. This would confirm the conclusions of Harris, Lewis and Vaughan that the hemolysin and the dermolysin are either the same substance or closely allied substances, and that they are independent of the Wassermann antibody.

Serum from the patient with cold hemagglutination paroxysmal hemoglobinuria and negative reactions to Wassermann and Donath-Landsteiner tests observed recently contained no such dermolysin. No wheal could be demonstrated on injection of his serum followed by the cold-warm treatment of the injection site in patient F.

When the new histamine-inhibiting drugs, such as diphenhydramine hydrochloride ("benadryl") and tripelennamine hydrochloride N.N.R. ("pyribenzamine") became available recently, studies were made on their effect on the action of the dermolysin present in the serum of patient F. While he received large doses (300 mg. orally in eight hours) of either diphenhydramine hydrochloride or tripelennamine hydrochloride, the action of the histamine was decidedly suppressed and much smaller urticarious wheals were raised than those obtained when he was not taking the drugs with the same technic. Besides a notable decrease in the size of the wheal, itching and erythematous flare were consistently absent. Neither diphenhydramine hydrochloride nor tripelennamine hydrochloride had any noticeable effect on patient F.'s hemoglobinuria.

TREATMENT OF SYPHILITIC PAROXYSMAL COLD HEMOGLOBINURIA

The treatment of choice of cold hemoglobinuria due to the cold-warm hemolysin is antisyphilitic therapy. Good results can be expected and have been reported from the use of arsenicals and the heavy metals. Kumagai and Namba[30] reported 10 clinical cures in 14 cases of syphilitic paroxysmal cold hemoglobinuria treated with arsenicals and heavy metals.

In the survey presented of 38 cases of syphilitic paroxysmal cold hemoglobinuria, results of antisyphilitic therapy are given in 25 of the reports. Fifteen of these cases were reported as clinically "cured" (no chills or dark urine during cold weather); 10 were reported as

30. Kumagai, T., and Namba, M.: Weitere Beiträge zur Kenntnis der paroxysmalen Hämoglobinurie, Deutsches Arch. f. klin. Med. **156**:257, 1927.

ameliorated in severity of reaction to cold, and none were reported as resistant to reportedly adequate antisyphilitic therapy.

Since only one report[31] concerning the use of penicillin in the treatment of syphilitic paroxysmal cold hemoglobinuria was found in the literature, it was decided to treat patient F. with the antibiotic substance. He was given penicillin intramuscularly, 20,000 units every three hours the first two days, 30,000 units every three hours the next two days and 40,000 units every three hours thereafter, to the total dose of 5,050,000 units.

He experienced no chills or dark urine since his discharge from the hospital seven months before this report, although he was outdoors frequently in below-freezing weather. However, moderate reactions to cold water exposure tests have occasionally occurred during the past six months, with dark urine and systemic reaction, though these reactions were not as severe as those elicited before the institution of penicillin therapy. Reactions to Donath-Landsteiner and Mackenzie tests at present also remain slightly positive, and his Wassermann and Kahn reactions are both still strongly positive.

It is not intended that a course of 5,000,000 units of penicillin be recommended as definitive treatment of syphilitic paroxysmal cold hemoglobinuria. Patients with this condition have the late form of syphilis and should be followed by weekly injections of oxophenarsine hydrochloride U.S.P. ("mapharsen") and bismuth as this patient is now receiving.

SUMMARY AND CONCLUSIONS

1. Syphilitic paroxysmal cold hemoglobinuria is a disease characterized by sudden onset of shaking chills, fever, abdominal distress, nausea and, frequently, evidences of Raynaud's disease, associated with passage of red to dark urine for four to ten hours after exposure to cold, owing to a cold-warm hemolysin in the patient's serum which, along with complement, attaches itself to the red blood cells in the cold, hemolyzing the red blood cells on subsequent warming.

2. This cold hemoglobinuria due to the cold-warm hemolysin is a manifestation of syphilis. It has not been reported in consistent connection with or as a counterpart of any disease other than syphilis.

3. Thirty-eight case reports were reviewed, and none of them revealed clinical manifestations of invasion of tissue by Treponema pallidum. Theoretic possibilities of the relation of the hemoglobinuric state to a state of immunity in syphilis are discussed. It is assumed that the cold-warm hemolysin appears only during the quiescent stage of the

31. Goldberg, L. C.: Treatment of Paroxysmal Hemoglobinuria with Penicillin, Am. J. Syph., Gonor. & Ven. Dis. **31**:163 (March) 1947.

late form of syphilis, when owing to natural immune defenses the spirochetes are not invasive.

4. There are two separate and distinct etiologic factors which can produce the symptom complex of "paroxysmal cold hemoglobinuria"—syphilitic paroxysmal cold hemoglobinuria and cold hemagglutination paroxysmal hemoglobinuria. Points of differentiation between the two conditions are presented. For diagnostic purposes the term "paroxysmal cold hemoglobinuria" is inadequate and should be abandoned.

5. Diphenhydramine ("benadryl") hydrochloride and tripelennamine hydrochloride ("pyribenzamine") were observed to be effective in reducing decidedly the urticarious reaction produced by the dermolysin present in the serum of a patient with syphilitic paroxysmal cold hemoglobinuria. These drugs had no apparent effect on the patient's intravascular hemolysis and hemoglobinuria.

6. A typical case of syphilitic paroxysmal cold hemoglobinuria is presented, with results of special laboratory investigation. Treatment with 5,000,000 units of penicillin resulted in a clinical "cure," for the patient has experienced no chills or dark urine, although he frequently works outdoors in below freezing weather. However, he still has a moderately positive reaction to the Mackenzie test and reacts adversely on occasion to cold water tests.

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IMPAIRMENT OF PULMONARY FUNCTION IN POLIOMYELITIS

Oximetric Studies in Patients with the Spinal and Bulbar Types

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IMPAIRMENT of respiration presents a serious therapeutic problem in poliomyelitis. Single or multiple involvement of the components of the respiratory mechanism frequently decreases the patient's arterial oxygen saturation in cases of the spinal and bulbar types during the acute and convalescent stages of the disease. Accurate diagnosis of the nature of the respiratory defect is an essential step in the treatment of the patient.

From a physiologic viewpoint, the various disturbances in pulmonary function in poliomyelitis may be resolved into two general types, ventilatory deficiency and alveolar deficiency. Defective ventilation may occur with paralysis of the diaphragm or of the intercostal muscles or with depression of the respiratory center. Alveolar deficiency, or inadequate gas transfer between the pulmonary alveoli and the blood, may result from parenchymal lesions in the lungs, e.g., pulmonary edema, atelectasis, focal hemorrhage and pneumonia. A similar classification was suggested in 1941 by Cournand and Richards[1] and more recently by Ornstein and his co-workers.[2] Both the ventilatory exchange and the alveolar transfer of gases may be deficient in cases of obstructive lesions of the upper airway.[3]

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1. Cournand, A., and Richards, D. W., Jr.: Pulmonary Insufficiency: I. Discussion of a Physiologic Classification and Presentation of Clinical Tests, Am. Rev. Tuberc. **44**:26, 1941.

2. Ornstein, G. C.; Herman, M.; Friedman, W. N., and Friedlander, E.: Pulmonary Function Tests, Am. Rev. Tuberc. **53**:306, 1946.

(Footnotes continued on next page)

Objective evaluation of impaired pulmonary function and appraisals of oxygen or respirator therapy were undertaken with the use of the Millikan-Smaller recording oximeter.[4] In this report the technic employed in these function studies will be presented, together with the findings in 8 patients with poliomyelitis. As a result of the application of these function studies to 43 patients during the epidemic, certain practical uses of oximetry have appeared and will be described.

METHODS

Changes in the arterial blood oxygen saturation were measured by means of the recording oximeter. This device consists essentially of a pair of photoelectric cells fixed in a mounting which can be attached to the pinna of the ear and allows a standard light source to activate the cells after passing through the ear and two selective filters. One filter allows light to pass at the wavelength for maximum selective absorption for reduced hemoglobin, and the other allows it to pass at a wavelength at which light is absorbed by both reduced hemoglobin and oxyhemoglobin to equal extents. By a suitable electrical arrangement described by Hemingway,[4e] it is possible to record quantitatively the changes in the fraction of hemoglobin present as oxyhemoglobin, or in the oxygen saturation.

It should be noted that there are certain errors[5] which enter into such measurements, the major one of which, from a practical viewpoint, is that due to edema of the ear developing while the earpiece is in place. In these studies errors from this source were not observed in less than three hours of use. Therefore continuous measurements were limited to that period.

In practice, the oximeter earpiece is attached to the patient's ear firmly to prevent spontaneous slippage. The light source is turned on for fifteen minutes to allow thermal equilibrium to occur before readings are begun. Since the oximeter does not allow one to determine the absolute value but only changes in

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3. (*a*) Brown, J. R., and Baker, A. B.: Poliomyelitis: I. Bulbar Poliomyelitis; Neurophysiological Interpretation of the Clinico-Pathological Findings, J. Nerv. & Ment. Dis., to be published. (*b*) Brown, J. R.; Baker, A. B.; Adams, J., and McQuarrie, I.: The Bulbar Form of Poliomyelitis: I. Diagnosis and the Correlation of Clinical with Physiologic and Pathologic Manifestations, J. A. M. A. **134:** 757-762 (June 28) 1947. (*c*) Priest, R. E.; Boies, L. R., and Goltz, M. F.: Tracheotomy in Bulbar Poliomyelitis, Ann. Otol., Rhin. & Laryng. **56:**250, 1947. (*d*) Kubicek, W. G.; Holt, G. W.; Elam, J. O.; Brown, J. R., and Gullickson, G.: Oxygen Therapy in Poliomyelitis: A Tracheotomy Inhalator, Arch. Phys. Med. **29:**217, 1948.

4. (*a*) Millikan, G. A.: The Oximeter, an Instrument for Measuring Continuously the Oxygen Saturation of the Arterial Blood in Man, Rev. Scient. Instruments **13:**434, 1942. (*b*) Smaller, B.: Report EXP-M-54-653-102 United States War Department, May 4, 1942; Report EXP-M-49-696-16, ibid., Aug. 28, 1942. (*c*) Hemingway, A., and Taylor, C. B.: Laboratory Tests of the Oximeter with Automatic Compensation for Vasomotor Changes, J. Lab. & Clin. Med. **29:**987, 1944. (*d*) Liston, M. D.; Quinn, C. E.; Sargeant, W. E., and Scott, G. G.: A Contact Modulated Amplifier to Replace Sensitive Suspension Galvanometers, Rev. Scient. Instruments **17:**194, 1946. (*e*) Hemingway, A.: A Physiologic Investigation of Events Occurring when Changing from Oxygen to Air at 55,000 Feet, J. Aviation Med. **15:**685, 1944.

oxygen saturation, it is necessary to know the initial value of oxygen saturation if changes are to be assigned absolute values. The initial value of arterial oxygen saturation can be obtained with absolute certainty only by direct measurement. In these studies it was frequently determined by the Van Slyke[6] manometric method or the Scholander-Roughton micromethod.[7] However, for most practical purposes it is fortunately unnecessary to make these time-consuming chemical measurements. It is more practical to assume tentatively that the arterial blood is fully saturated after prolonged breathing of 100 per cent oxygen when the minute respiratory volume is normal. This assumption is obviously invalid in severe alveolar deficiency (and in the presence of anomalies of the great vessels), but no false deductions ordinarily result from this error. Consequently in these studies the oximeter recorder was usually set at 100 per cent when the patient was adequately ventilated with 100 per cent oxygen for ten minutes. In few instances did the chemically measured oxygen saturation differ from the assumed value by more than 2 per cent.

OBSERVATIONS

I. SPINAL INVOLVEMENT

CASE 1.—*Severe Ventilatory Deficiency in Spinal Poliomyelitis.*—M. P., a 24 year old white woman, was admitted to University Hospitals on Aug. 3, 1946, after the onset of paralysis of the intercostal muscles. Paralysis of the diaphragm and of the lower extremities occurred on August 8. The patient was placed in a respirator.

By August 22 there had been no clinical improvement. The patient had remained in the respirator constantly. A function test for ventilatory deficiency indicated severe impairment (fig. 1*A*). Opening of the respirator ports to render the respirator pressure ineffective and allow the patient to attempt ventilation independently was followed by a precipitous decrease in saturation, which was promptly restored to 90 per cent when the ports were closed. The remainder of the test represents evaluation of treatment. Obviously the repeated opening of the respirator ports, which was necessary for routine care, was inflicting multiple episodes of anoxia. Accordingly the protection afforded by the administration of oxygen when the ports were open was determined. When oxygen was given at the instant the ports were closed the saturation quickly returned to 95 per cent. However, if oxygen was administered at the time the ports were opened the saturation decreased

5. It was found that electrical artefacts which appeared on the tracing as rapid irregular excursions of the recorder pen could be entirely eliminated by suitable grounding of the high gain amplifier being used. The formation of local edema at the site of the oximeter earpiece caused another artefact consisting of a gradual downward drift in the recorded value in tests of several hours' duration. To determine the presence and the magnitude of this artefact, the conditions of the previously recorded reference saturation were duplicated and the resulting saturation compared with the reference value. Unfortunately the only available earpiece, an adult size, excluded the use of oximetry for patients with small ears.

6. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

7. Scholander, P. F., and Roughton, F. J. W.: Micro Gasometric Estimation of the Blood Gases: I. Oxygen, J. Biol. Chem. **148**:541, 1943.

only 5 per cent within eight minutes, whereas without oxygen the saturation had decreased 15 per cent within one minute.

Pronounced ventilatory deficiency persisted (fig. 1*B*). It was found that the maximal protection against the hypoxia due to suspension of the artificial respiration was attained by giving oxygen for five minutes before the ports were opened as well as while they were opened. In this way the patient achieved full saturation before ventilation was essentially stopped. Under these conditions the patient could tolerate suspended ventilation for a period of eight minutes, with the arterial oxygen saturation remaining about 98 per cent. At the end of eight minutes she experienced mild dizziness which was associated with hypercapnia.

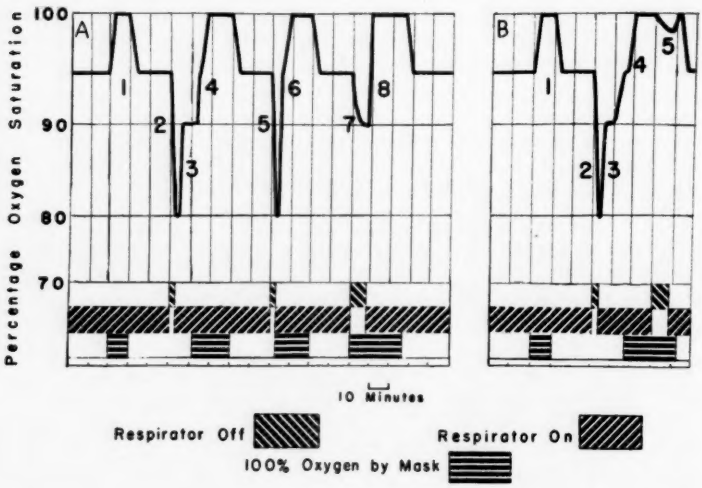

Fig. 1.—Function tests in a patient in a respirator with paralysis of the diaphragm and the intercostal muscles. Reference saturation in both tests at 95 per cent with the patient in the respirator and breathing air. The patient had been in the respirator for three weeks (*A*) and for six weeks (*B*) when the respective tests were done. Note the rapid onset of hypoxia, a decrease of 15 per cent in the saturation within one minute, when the use of the respirator was momentarily discontinued (*2* and *5* in *A* and *2* in *B*). The response would have been considerably greater in each instance had not the respirator been started when the saturation reached 80 per cent. This finding is typical of severe ventilatory deficiency. From a comparison of *3* and *6* in *A* and *3* in *B* it is apparent that the saturation could be restored to normal more rapidly if oxygen were administered when the respirator was started (or when the ports were closed). However, when oxygen was given at the time the use of the respirator was discontinued (*7* in *A*), the resulting hypoxia was limited to a 5 per cent decrease within eight minutes. In *B* note that twelve minutes were required for the saturation to return to normal when the respirator alone was used. In the same diagram *5* indicates that the maximal protection against the hypoxia due to the discontinuation of the use of the respirator was obtained when the patient received oxygen before the ports were opened. In this instance the saturation decreased only 2 per cent during the eight minutes the patient was without artificial respiration.

Case 2.—*Mild Ventilatory Deficiency in Spinal Poliomyelitis.*—E. K., a 17 year old white girl, experienced onset of weakness of the diaphragm and of the inter-

costal muscles on Aug. 10, 1946, the third day of illness. She was admitted to University Hospitals and placed in a respirator.

On August 11 she was given a trial out of the respirator under clinical observation. Fatigue developed after four minutes. By September 6 the periods out of the respirator had been gradually increased on the basis of clinical impression until the patient was being allowed to breathe independently for sixty-four minutes daily. A function study was started at the end of this sixty-four minute period to determine objectively whether she could tolerate additional time out of the respirator without suffering hypoxia. It was found that she was able to maintain a normal arterial oxygen saturation for four hours and fifty-nine minutes without

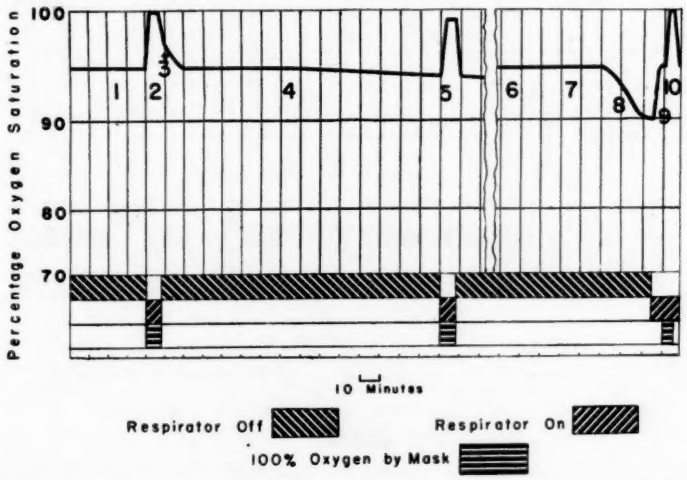

Fig. 2.—Function test in a patient in a respirator with incomplete paralysis of the diaphragm and the intercostal muscles. Reference saturation at 95 per cent with the patient out of the respirator and breathing air. When this test was carried out the patient had been in the respirator for four weeks because of weakness of the diaphragm and of the intercostal muscles. She had been out of the respirator for sixty-four minutes when the test was started. No significant change in the recorded saturation occurred until she had been out of the respirator for four hours and fifty-nine minutes, when a decrease of 5 per cent was recorded (*8*). This finding indicated a mild ventilatory deficiency. When the respirator was started the saturation returned to 95 per cent (*9*), and the administration of 100 per cent oxygen gave a normal saturation response of 100 per cent. Chemical analysis of arterial blood showed an oxygen saturation of 97 per cent (*3*). For calibration, 100 per cent oxygen was given for a brief period while the respirator was turned on (*2, 5,* and *10*).

artificial respiration (fig. 2). At the end of this period the saturation decreased gradually from 95 to 90 per cent and remained stabilized until the respirator was started. She experienced no distress or fatigue at this time. Accordingly she was started on a schedule of three hours out of the respirator daily, with frequent increases in this period on the basis of repeated ventilatory function tests. By September 27 the patient was able to be out of the respirator without suffering hypoxia for fourteen hours daily. On October 5 the use of the respirator was discontinued.

II. BULBAR INVOLVEMENT

CASE 3.—*Alveolar Deficiency in Acute Bulbar Poliomyelitis.*—D. T., a 13 year old white boy, was admitted to University Hospitals on Aug. 17, 1946, with the history of acute bulbar symptoms for three days. Tracheotomy was performed on admission, and the use of 50 per cent oxygen by tracheotomy inhalator[3d] was started.

On August 23 intermittent apnea developed and the patient was placed in a respirator. A function study was started two hours later. At this time the apnea

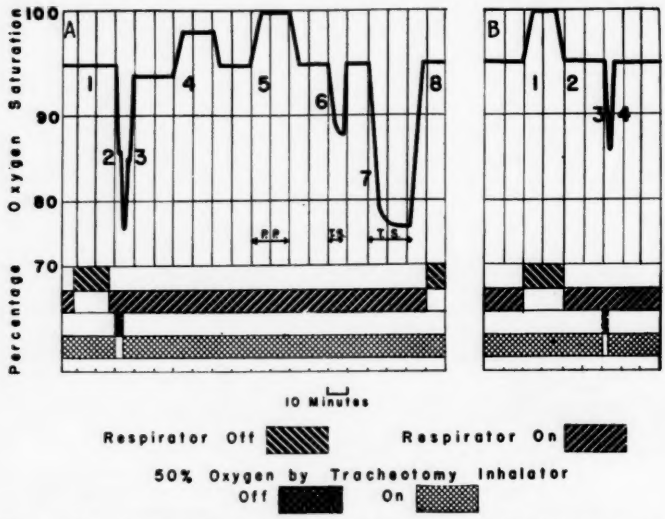

Fig. 3.—Function tests in a patient who had undergone tracheotomy and who required the respirator because of apnea. Reference saturation at 95 per cent with the patient in a respirator and breathing 50 per cent oxygen by tracheotomy inhalator. The symbols *P P* indicate positive pressure during expiration; *T. S.* refers to tracheotomy tube suction. The patient had severe bulbar involvement for five days before the first test (*A*) was done. Treatment had consisted of tracheotomy, administration of 50 per cent oxygen by tracheotomy inhalator and the use of the respirator for control of apnea. Since no changes occurred in the saturation when the respirator was discontinued (*1* and *8* in *A*), no ventilatory deficiency is demonstrated. However, when air was substituted for the 50 per cent tracheal oxygen, severe hypoxia developed rapidly (*2* in *A*). The use of positive pressure of 3 cm. of water during expiration was found to increase the saturation either when the nose was occluded (*4* in *A*) or when 100 per cent oxygen was given by mask (*5*). Suction of the tracheotomy tube (*6* and *7*) produced hypoxia, which in one instance was extended over a period of twenty-eight minutes. This test indicated alveolar deficiency. The second test (*B*) was carried out three days later and showed an actual increase in saturation when the use of the respirator was discontinued (*1* in *B*). It was noted that the patient's own respiratory rate was 32 per minute and the respirator was being operated at 18 cycles per minute. Substituting air for 50 per cent tracheal oxygen (*3* in *B*) revealed persisting alveolar deficiency.

apparently had been successfully controlled. No changes occurred in the arterial oxygen saturation when the patient was allowed to breathe independently (fig. 3*A*). No ventilatory deficiency was demonstrated. However, when the patient breathed air instead of the 50 per cent oxygen there was a rapid onset of hypoxia, which

indicated a definite alveolar deficiency. During the rest of this test the patient's reaction was evaluated. When 50 per cent oxygen was administered by tracheotomy inhalator with a positive pressure of 3 cm. of water during expiration there was a 3 per cent increase in saturation. In order to render this pressure effective it was necessary to occlude the nose (see 4 in figure 3*A*). When this pressure was used during the administration of 100 per cent oxygen by mask, the saturation increased 5 per cent. The routine tracheotomy tube suction which had been ordered every fifteen minutes for the removal of accumulated secretions resulted in considerable hypoxia. In one instance the hypoxia due to tracheotomy tube suction was extended over a period of twenty-eight minutes.

By August 27 the patient had improved. He had been left in the respirator because of the risk that apnea might recur. However, the return of function of the respiratory center resulted in an asynchronism between the patient's respiratory rate of 32 per minute and the 18 cycles per minute of the respirator. During another function study (fig. 3*B*), it was found that the patient actually increased his arterial oxygen saturation by 5 per cent when the respirator was turned off. A trial without 50 per cent oxygen by tracheotomy inhalator again indicated alveolar deficiency. For this reason oxygen therapy was continued. The use of the respirator was discontinued and was not required further during his course in the hospital.

By September 9 he was able to maintain a normal oxygen saturation while breathing air, which indicated that there was no further need for oxygen therapy. Oximetry was employed subsequently as a basis for removal of the tracheotomy tube.

CASE 4.—*Severe Alveolar Deficiency in Acute Bulbar Poliomyelitis.*—C. S. U., a 22 year old white man, was admitted to the hospital on Aug. 25, 1946, the seventh day of acute bulbar symptoms. There was a history of dysphagia, regurgitation of fluid through the nose, choking and difficulty in speech of two days' duration. Tracheotomy was performed immediately, and the use of 50 per cent oxygen by tracheotomy inhalator was started.

On August 25 cyanosis suddenly developed when the flow of oxygen through the inhalator was momentarily interrupted. During this brief interval, he was breathing ambient air. Frothy pink fluid drained from the nose, the mouth and the tracheotomy tube. Loud gurgling rales were grossly audible. Suction of the tracheotomy tube yielded 75 cc. of edema fluid. Administration of oxygen by positive pressure was started immediately. A pressure of 12 cm. of water was applied during inspiration by manual compression of the rubber breathing reservoir bag (similar to the technic commonly used in anesthesia). An expiratory positive pressure of 12 cm. of water was also used in the inhalator. One hundred per cent oxygen was given concomitantly by mask.[8d] The patient's color promptly returned to normal, and after thirty minutes of this therapy no rales could be detected over the pulmonary fields. It was found that when oxygen therapy was discontinued and the patient allowed to breathe air the arterial oxygen saturation decreased more than 15 per cent rapidly (fig. 4). This finding established the presence of alveolar deficiency since there was no evidence that ventilation was impaired. The additional data were for the purpose of evaluating treatment. When 50 per cent oxygen was given via inhalator with a positive expiratory pressure of 4 cm. of water but without occlusion of the nose, a saturation of 95 per cent was recorded. Occlusion of the nose resulted in a gradual increase in the saturation to 98 per cent, and this value was not further increased by the use of 100 per cent oxygen by mask (in addition to the 50 per cent oxygen by

tracheotomy inhalator). If these same concentrations of oxygen were continued by trachea and by mask without any positive pressure, the saturation decreased to 90 per cent. On this basis it was decided to continue the administration of 100 per cent oxygen by mask and of 50 per cent oxygen by tracheotomy inhalator with a positive pressure of 4 cm. of water during expiration. In order to protect the patient against fatigue resulting from the expiratory resistance, a pressure

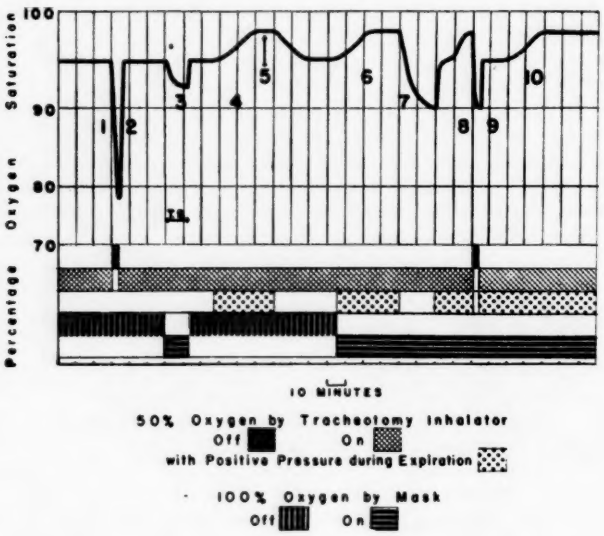

Fig. 4.—Function test in patient who had undergone tracheotomy after recovery from acute pulmonary edema. Reference saturation at 95 per cent with the patient breathing 50 per cent oxygen by tracheotomy inhalator with a positive pressure of 4 cm. of water during expiration (nose not occluded). The patient had been acutely ill for twelve days when this test was done. Treatment had consisted of tracheotomy and of administration of 50 per cent oxygen by inhalator. Positive pressures of 12 cm. of water during inspiration and expiration had been used for thirty minutes just prior to the test in order to reverse the pulmonary edema. Note the rapid onset of hypoxia when oxygen therapy was discontinued and the patient allowed to breathe air without resistance (*1*). This reveals the presence of alveolar deficiency. In evaluation of treatment, it was found that the hypoxia resulting from suction of the tracheotomy tube could be essentially eliminated by the administration of 100 per cent oxygen by mask and by continuing the flow of oxygen through the inhalator during this time (*3*).[3d] The symbols *T. S.* indicate the period during which suction was applied to the tracheotomy tube. The use of positive pressure during expiration resulted in an increase of the saturation from 95 to 98 per cent either when the nose was occluded (*4*) to render the pressure effective or when 100 per cent oxygen was given by mask (*6*). Arterial blood was found by chemical analysis to have an oxygen saturation of 98.1 per cent (*5*). When the same concentrations of oxygen were continued through mask and inhalator without positive pressure the saturation decreased 8 per cent (*1*). The difference between *3* and *8* indicates the advantage of continuing the flow of oxygen through the inhalator when suction of the tracheotomy tube is required. In *8* the tracheotomy inhalator was detached, so that the patient breathed air through the tracheotomy opening, but the use of 100 per cent oxygen by mask was continued. Note the prolonged saturation responses (*4, 6* and *10*).

vest was used intermittently. This method of artificial respiration produces active expiration and passive inspiration. The pressure vest is similar in principle to the Bragg-Paul pulsator commonly used in England.

CASE 5.—*Prolonged Alveolar Deficiency in Convalescent Bulbar Poliomyelitis.*—E. M., a 25 year old white man, was admitted to the hospital on Aug. 19, 1946, with a partial laryngeal obstruction. Tracheotomy was performed immediately.

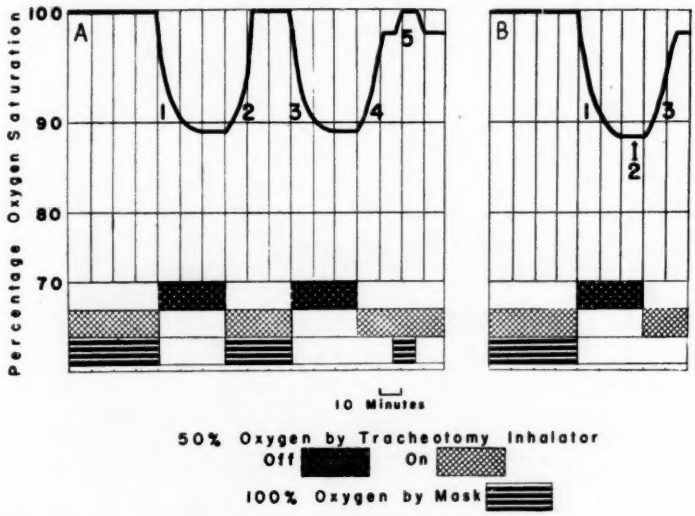

Fig. 5.—Function tests in a patient who had undergone tracheotomy on the thirteenth and twenty-fifth days in the hospital. Reference saturation at 100 per cent with patient breathing 100 per cent oxygen by mask and 50 per cent oxygen by tracheotomy inhalator. On both occasions the patient suffered a mild hypoxia when allowed to breathe air (*1* and *3* in *A* and *1* in *B*). Note that the saturation responses as well as the saturation times were increased, which indicated a persisting alveolar deficiency. An arterial sample was found by chemical analysis to have a saturation of 89.7 per cent (*2* in *A*). Under the conditions of treatment a saturation of 98 per cent was being maintained by the use of 50 per cent oxygen in the tracheotomy inhalator (after *5* in *A* and *3* in *B*).

Administration of 50 per cent oxygen by tracheotomy inhalator was started. He was acutely ill, with periods of coma, delirium and disorientation.

By August 26 the acute phase of bulbar involvement had apparently subsided and the patient showed much improvement. He had remained free of ventilatory impairment. The question of how long oxygen therapy should be continued was studied by means of repeated function tests. At this time it was found that the arterial oxygen saturation was 89 per cent when the patient breathed air, which indicated a mild alveolar deficiency (fig. 5*A*). The patient noticed no distress during this period of hypoxia. A saturation of 98 per cent was being maintained by the use of 50 per cent oxygen in the tracheotomy inhalator.

After twenty-five days in the hospital the patient still required oxygen therapy, as shown by a repeated function test (fig. 5*B*). The hypoxia which accompanied the substitution of air for the 50 per cent oxygen by tracheotomy inhalator was

essentially the same as that previously recorded. On the thirty-ninth day the patient demonstrated a normal arterial saturation while breathing air. Accordingly oxygen therapy was discontinued.

CASE 6.—*Adequate Ventilatory and Alveolar Function in Convalescent Bulbar Poliomyelitis.*—A. P., a 31 year old white man, was admitted to the hospital on Oct. 2, 1946, the ninth day of his acute illness. On October 3 difficulty in swallow-

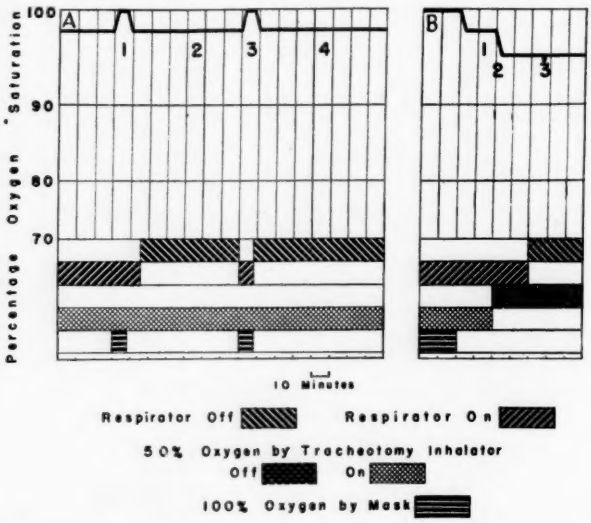

Fig. 6.—Function tests in a patient who had undergone tracheotomy and who required artificial respiration for control of apnea. Reference saturation at 98 per cent with patient in respirator and breathing 50 per cent oxygen by tracheotomy inhalator. These tests were carried out on the fourteenth and sixteenth days of illness. Treatment had consisted of tracheotomy and of administration of 50 per cent oxygen by tracheotomy inhalator. The first test (*A*) demonstrated the absence of ventilatory deficiency since the saturation remained constant when the respirator was discontinued (*2* and *4*). This finding was confirmed in the second test (*B*), in which it was also shown that the patient had no alveolar deficiency. When oxygen therapy was discontinued the saturation decreased to the normal 95 per cent (*2*). Arterial blood showed an oxygen saturation of 96.5 per cent as determined by chemical analysis (*3* in *B*). Note that the saturation time as well as the saturation response is within normal limits.

ing, mild cyanosis and anoxic euphoria occurred. Tracheotomy was performed, and administration of 50 per cent oxygen by tracheotomy inhalator was started, a positive pressure of 3 cm. of water being employed during expiration. A function test at this time for evaluation of treatment indicated that a normal saturation was being maintained.

On September 4 irregular diaphragmatic excursions developed, which suggested depression of the respiratory center. The patient was placed in a respirator. A function test on September 7 showed no ventilatory deficiency (fig. 6*A*) since there was recorded no change in the arterial oxygen saturation when the use of the respirator was discontinued. However, because of the risk of fatigue or of

recurrence of apnea the patient was left in the respirator. On September 9 a function test indicated a normal saturation when the use of both the respirator and oxygen therapy was discontinued; this indicated the absence of both ventilatory and alveolar deficiency (fig. 6*B*).

III. BULBOSPINAL INVOLVEMENT

CASE 7.—*Alveolar Deficiency in Acute Bulbospinal Poliomyelitis.*—F. L. W., a 28 year old white man, experienced the onset of acute spinal symptoms on Sept. 7, 1946. He was admitted to University Hospitals on September 8. No disturbance in respiration existed at this time.

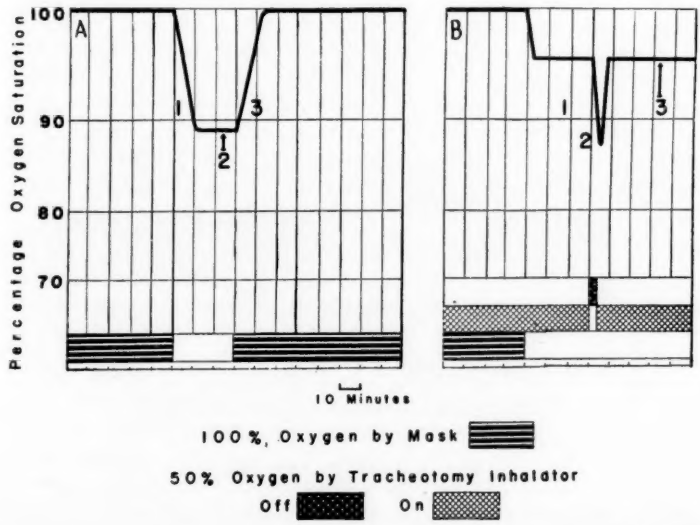

Fig. 7.—Function tests in patients with acute bulbospinal poliomyelitis before and after tracheotomy. Reference saturation at 100 per cent with the patient breathing 100 per cent oxygen by mask for fifty minutes. The first test (*A*) was carried out twenty-four hours prior to tracheotomy. The second test (*B*) was done three hours after tracheotomy. Note the hypoxia in (*A*) and the increase in saturation time when the inspired air was changed from 100 per cent oxygen to air (*1*). Arterial blood revealed a saturation of 89.5 per cent (*2*). These findings established a definite alveolar deficiency, since ventilation was not impaired. In the subsequent test it was found that under the conditions of treatment a normal (95 per cent) saturation was being maintained (*1* in *B*). Chemical analysis of arterial blood showed a saturation of 95.3 per cent (*3*). This test confirmed the presence of alveolar deficiency (*2*).

On September 15 complete paralysis of all extremities occurred; there was a definite weakness of the intercostal muscles. Ventilation was not impaired, however. On September 17 a mild irritability developed, which suggested hypoxia. There was no cyanosis or dyspnea. A function test was carried out to determine the presence of alveolar deficiency since ventilation was still adequate. It was found that the patient's arterial oxygen saturation was 89 per cent while he breathed air (fig. 7*A*). The administration of 100 per cent oxygen by mask

increased the recorded value to 100 per cent, but this required twelve minutes. The increase in saturation time and the response indicated a definite alveolar deficiency. On the basis of these findings, oxygen therapy was started, but the patient became irrational and combative. For this reason attempts to give oxygen by mask and later by nasal catheter were unsuccessful.

By September 18 bulbar involvement could be definitely established since difficulty in swallowing and in speech, irregular respiratory rhythm and occasional diaphragmatic flutter developed, which suggested depression of the respiratory

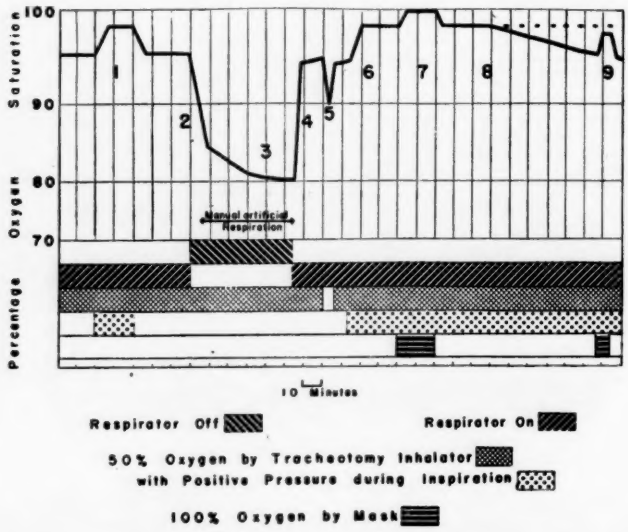

Fig. 8.—Function test in patient with acute bulbospinal poliomyelitis who had undergone tracheotomy and was in a respirator. Reference saturation at 95 per cent with the patient in respirator and receiving 50 per cent oxygen by tracheotomy inhalator with a positive pressure of 4 cm. of water during expiration. Note that the use of a positive pressure of 8 cm. of water during inspiration increased the saturation to 98 per cent (*1*). The decrease in saturation seen at *2* was due to discontinuation of the use of the respirator when the rubber neckpiece accidentally slipped loose. Manual artificial respiration was carried out during the forty-five minutes indicated, with the patient remaining in the respirator (*3*). This finding confirmed the presence of ventilatory deficiency. When oxygen therapy was discontinued for three minutes (*5*) the saturation fell rapidly but was not allowed to proceed. Thus alveolar deficiency is also demonstrated. The use of positive pressure of 8 cm. of water during inspiration was continued for the remainder of the test. The addition of 100 per cent oxygen by mask increased the saturation only 2 per cent (*7*). The dotted line indicates the actual saturation value corrected for drift artefact demonstrated to be *2* per cent (*9*).

center. Tracheotomy was performed, and administration of 50 per cent oxygen by tracheotomy inhalator was started. A function study after tracheotomy indicated that under the conditions of treatment a normal arterial oxygen saturation was being maintained (fig. *7B*). Because tracheotomy and effective oxygen therapy had relieved the patient's hypoxia, his alveolar deficiency appeared to

have been associated with a partial laryngeal obstruction which had contributed toward the development of a subacute pulmonary edema.

CASE 8.—*Ventilatory and Alveolar Deficiency in Acute Bulbospinal Poliomyelitis.*—M. B., a 31 year old white man, was admitted to the hospital on Aug. 20, 1946, the third day of acute spinal symptoms. He was placed in a respirator on his admission. On August 21 complete laryngeal obstruction developed, which led immediately to deep cyanosis and extensive pulmonary edema. After laryngeal intubation with a Mosher tube and aspiration of 200 cc. of foamy serous fluid, 100 per cent oxygen was insufflated through the Mosher tube while an emergency tracheotomy was performed. During this time it was observed that the action of the respirator apparently increased the severity of the patient's pulmonary edema, as indicated by the amounts of fluid aspirated from the trachea. For this reason the use of the respirator was discontinued and oxygenation was maintained by oxygen insufflation alone. Slight cyanosis persisted during this time. On completion of the tracheotomy, the respirator was started and 100 per cent oxygen was administered with a positive pressure of 12 cm. of water during inspiration and expiration through the tracheotomy inhalator until the patient's color returned to normal. At this time the inhalator mixture was changed to 50 per cent oxygen, and a function test was made to determine how adequate oxygenation could be maintained. A positive pressure of 4 cm. of water during expiration with 50 per cent oxygen through the inhalator was found to be satisfactory.

The results of a follow-up function test on August 21 for the purpose of evaluating both pulmonary deficiency and treatment are shown in figure 8. It was found that the use of 8 cm. of positive pressure during inspiration increased the saturation 3 per cent. At this juncture an accidental slipping of the rubber neckpiece of the respirator occurred, and the resulting leak rendered the respirator ineffective. A period of fifty-eight minutes was required to reattach the neckpiece. During the first eight minutes of this period the patient's saturation decreased to 84 per cent. A modified Schaeffer method of artificial respiration had been started when the saturation reached 90 per cent. For an interval of forty-eight minutes 18 compressions per minute of the anterior part of the thoracic wall by two operators (each with one hand extended through a respirator port) maintained the saturation above 80 per cent. The patient's saturation returned to normal promptly when the respirator was started. Thus he had pronounced deficiency of ventilatory function. The decrease in saturation that occurred when air was substituted for 50 per cent oxygen by tracheotomy inhalator was not followed below 90 per cent because of the previous inadvertent hypoxia. This response was sufficient to establish the presence of alveolar deficiency, however. During the remainder of the test the positive inspiratory pressure of 8 cm. of water was found to maintain a saturation of 98 per cent when 50 per cent oxygen by tracheotomy inhalator was administered, with the nose occluded. The addition of 100 per cent oxygen by mask increased the saturation to 100 per cent.

COMMENT

During the epidemic the aforementioned tests were used repeatedly to study pulmonary function in 43 patients. The recording oximeter has

proved to be a valuable clinical tool for evaluating ventilatory and alveolar deficiency.

The high incidence of hypoxia in patients with acute poliomyelitis of spinal, bulbar and bulbospinal types and in convalescent patients has not received sufficient attention previously. The significance of hypoxia during any stage of this disease is obvious from the viewpoint of effective treatment involving optimal conditions for the survival of viable neurons.[8] The differentiation between ventilatory and alveolar deficiencies in poliomyelitis has therapeutic implications of prime importance. For example, for a patient with alveolar impairment and without ventilatory deficiency in whom there is an inability to absorb adequate oxygen from the air, artificial respiration is ineffective because it merely guarantees an adequate ventilation and does not increase significantly oxygen tension in the alveoli. It should be recognized that neither oxygen therapy nor artificial respiration is successful in the presence of obstruction of the upper airways until patency is reestablished.[9]

The evaluation of pulmonary deficiency need not be limited to clinical impression. Observation of the adequacy of diaphragmatic and thoracic excursions affords only a crude estimation. The ability of the patient to remain free of cyanosis is an unreliable index of adequate oxygenation. Determinations of vital capacity, tidal air volume and respiratory minute volume and various indexes of ventilatory reserve[1] may be employed for the detection of ventilatory deficiency. Alveolar function as well as ventilatory function may be assayed by oximetry or by chemical analysis of the arterial blood for oxygen saturation. Oximetric procedures are advantageous because of their convenience for obtaining results immediately during different conditions and because ventilatory deficiency, alveolar deficiency and treatment may be evaluated during a single procedure. By the routine use of tests similar to those herein reported the causes of repeated hypoxic episodes during the attack of poliomyelitis may be detected and sometimes prevented. Reduced arterial oxygenation may exist in the absence of the classic signs and symptoms of anoxia. Changes in oxygen saturation recorded from the ear are presumably paralleled by changes in other blood vessels, including those of the nervous system. The instantaneous record of the

8. Wright, E. B.: Comparative Study of Effects of Oxygen Lack on Peripheral Nerve, Am. J. Physiol. **147**:78, 1946. Heinbecker, P.: Effect of Anoxemia, Carbon Dioxide and Lactic Acid on Electrical Phenomena of Myelinated Fibers of the Peripheral Nervous System, ibid. **89**:58, 1929. Gerard, R. W.: The Response of Nerve to Oxygen Lack, ibid. **92**:498, 1930. Schmitt, F. O.: On the Oxidative Nature of the Nerve Impulse, ibid. **95**:650, 1930.

9. Grulee, C. G., Jr., and Panos, T. C.: Epidemic Poliomyelitis in Children: Clinical Study, with Special Reference to Symptomatology and Management of Bulbar Polioencephalitis, Am. J. Dis. Child. **75**:24 (Jan.), 1948.

changes in arterial oxygen saturation detects the presence of hypoxia before the patient is subjected to fatigue, dyspnea or other undesirable symptoms. In none of the tests conducted was the duration of hypoxia resulting from the test procedures prolonged to the point of onset of cyanosis. Both the duration and the degree of hypoxia may be arbitrarily limited as desired. Obviously oximetry cannot be applied accurately in the evaluation of pulmonary function in the presence of grossly impaired cardiocirculatory function or in the presence of an abnormal oxygen-carrying capacity of hemoglobin, such as occurs in anemia. The tests described are not intended to provide an index of pulmonary reserve function but are useful for detecting deficiency under resting conditions.

The following procedures are recommended for tests of pulmonary function in patients with poliomyelitis and for determining the requirements of oxygen therapy and respirator treatment. One hundred per cent oxygen is administered by mask for ten minutes to a patient before he is placed in a respirator. The oximeter is set at 100 per cent. Administration of oxygen is prolonged for some minutes while recording is continued. If the saturation does not change, the mask is removed and the patient allowed to breathe room air. The saturation falls both in normal subjects and in patients with poliomyelitis when this maneuver is carried out. However, if the fall is greater than 8 per cent, it is presumed that there is abnormality. If the fall is greater than this, the patient is placed in a respirator and 100 per cent oxygen is administered again. The fall which occurs when a change to room air is made is studied again at several levels of ventilation. If the fall in saturation with normal or supernormal values of respiratory minute volume (with the change from 100 per cent oxygen to air) is 8 per cent or less, the patient was probably suffering from simple ventilatory deficiency while out of the respirator. If the decline in saturation with the foregoing maneuver is greater than 8 per cent, the patient is probably in a state of alveolar deficiency, the degree being proportional to the magnitude of the fall. Since arterial oxygen saturations below 80 per cent are potentially deleterious, even for short periods, the value is not allowed to fall below that level.

The presence of combined ventilatory and alveolar deficiency can be detected by determining whether the patient suffers a decline in oxygen saturation of more than 8 per cent on changing from 100 per cent oxygen to room air and also whether there is a fall when artificial respiration is stopped. For a practical test, one can determine first the fall in oxygen saturation when a change is made from oxygen to room air with the patient in the respirator. If it is greater than 8 per cent, the oxygen percentage in the inspired air can be increased gradually until the saturation is 92 per cent. Then the use of the respirator can be stopped and

a change in saturation noted. A requirement of more than 20 per cent oxygen and a fall in saturation under the foregoing conditions establishes combined alveolar and ventilatory deficiency.

The ability of patients to tolerate removal from the respirator is tested by establishing first the oxygen saturation while the patient is breathing room air. The saturation is then recorded continuously while the use of the respirator is discontinued. The respiratory efforts and the saturation record are both observed continuously, and the respirator is restarted when the saturation has fallen to 85 per cent. This test, without danger to the patient, distinguishes between the apprehensive patient who can actually tolerate long periods without the respirator and the patient with severe, true ventilatory deficiency. It also permits the physician to reassure the apprehensive patient, with the fortification of an objective measure of respiratory efficiency to guide his treatment.

Certain suggestions with respect to the treatment of patients with poliomyelitis who have disturbances in respiration are evident from the findings obtained in this series of function tests.

SUMMARY

Oximetric procedures to detect ventilatory deficiency, alveolar deficiency and the adequacy of treatment have been described. The findings in 8 patients with poliomyelitis of the spinal, bulbar and bulbospinal types have been presented.

These findings suggest the following conclusions regarding treatment:

1. Patients with severe ventilatory deficiency in respirators suffer hypoxia rapidly when the respirator ports are opened. This may be delayed by administration of 100 per cent oxygen by mask for a period of five minutes before the ports are opened until they are closed.
2. Oximetry provides a basis for safely liberating a convalescent patient from the respirator. The distinction between apprehensiveness on the part of the patient and genuine ventilatory deficiency can be made with assurance. The maximum safe limit of time for release from the respirator can be measured.
3. When the patient in a respirator is unable to synchronize his respiratory rate and rhythm with that of the respirator, the result may interfere with effective ventilation.
4. Patients with respiratory impairment of undemonstrable cause may be found on oximetric study to have hypoxia in the absence of frank clinical signs or symptoms. One such patient reported on showed a decreased arterial oxygen saturation twenty-four hours before a definite laryngeal obstruction was diagnosed. Tracheotomy and effective oxygen therapy relieved the hypoxia

for which oxygen by mask and nasal oxygen therapy had been unsuccessful.

5. Routine tracheotomy tube suction for removal of accumulated secretions may produce severe hypoxia. In some cases this has been minimized by giving 100 per cent oxygen by mask and continuing the flow of oxygen through the tracheotomy inhalator during the interval of the suction procedure.
6. A modified method of the Schaeffer type of artificial respiration used for a patient remaining in the respirator was found to sustain an arterial oxygen saturation 15 per cent below that afforded by the respirator.
7. A small fraction of patients convalescent from poliomyelitis required oxygen therapy for as long as six weeks. Clinical indications of lack of oxygen were absent when the patients breathed air although a definite hypoxia was demonstrated by oximetry.
8. Increase of the pulse rate occurred with mild hypoxia and was a useful clinical indication for oxygen therapy.

Drs. A. B. Baker and Irvine McQuarrie, of the Minnesota Poliomyelitis Research Commission, and Drs. H. S. Wells, W. G. Kubicek, G. W. Holt, E. B. Brown and A. H. Sussman cooperated and assisted in this work. Miss Mary Lou Smersh gave technical assistance. Apparatus was loaned to the University of Minnesota by the American Air Force School of Aviation Medicine, Randolph Field, the Aeromedical Laboratory at Wright Field, the Aeromedical Laboratory of the Mayo Foundation and the Perkin-Elmer Corporation, Glenbrook, Conn. Cooperation in obtaining equipment by rapid delivery during the epidemic was furnished by the Coleman Instrument Company, Maywood, Ill., General Motors Laboratory, Detroit, and the Leeds and Northrup Co., Philadelphia.

CIRRHOSIS FOLLOWING INFECTIOUS HEPATITIS

A Report of Five Cases, in Two of Which There Was Superimposed Primary Liver Cell Carcinoma

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ATLANTA, GA.

IN AN APPRECIABLE number of cases infectious hepatitis leaves clinical evidence of impaired hepatic function and in some instances manifests itself as a chronic, probably progressive, disease. We believe that in some cases the morphologic pattern of its late stages is distinct, although its clinical course is indistinguishable from that of Laennec's cirrhosis or acute hepatic failure.

In this report we present 5 cases in which cirrhosis, we believe, resulted from infectious hepatitis. Primary liver cell carcinoma developed in 2 of these. In 4 the cirrhosis was clinically indistinguishable from Laennec's cirrhosis; the morphologic findings ruled out this diagnosis, and the fundamental lesion of the liver was identical with that described by F. B. Mallory as "toxic cirrhosis." Our few cases, however, do not preclude types of lesions other than that reported here as end results of infectious hepatitis.

Observations concerning the outcome of infectious hepatitis have resulted in two opposed patterns of thought. Lucké[1] has concluded on the basis of his observations that complete restoration of hepatic parenchyma occurs in nonfatal cases of the disease. On the other hand, the literature contains many demonstrations that the functional integrity of the liver is not restored after a bout of hepatitis. Kornberg,[2] Soffer

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1. Lucké, B.: The Structure of the Liver After Recovery from Epidemic Hepatitis, Am. J. Path. **20**:595-620 (May) 1944.

2. Kornberg, A.: Latent Liver Disease in Persons Recovered from Catarrhal Jaundice and in Otherwise Normal Medical Students as Revealed by the Bilirubin Excretion Test, J. Clin. Investigation **21**:299-308 (May) 1942.

and Paulson[3] and Altschule and Gilligan,[4] as well as many others, have emphasized the functional impairment that persists for a long time after infectious hepatitis, without symptomatic or obvious clinical evidence of hepatic disease. Pratt and Stengel[5] and Bloomfield,[6] as well as many authors writing since the recent outbreaks (Barker and associates[7]; Fox and associates[8]; Klatskin and Rappaport[9]; Neefe[10]; Kelsall and associates[11]), have emphasized the obviously chronic nature of hepatitis in some cases, correlating it with clinical and laboratory evidence of hepatic dysfunction.

This concept that infectious hepatitis may produce permanent residual injury of the liver is further supported by a number of morphologic observations. Some Scandinavian authors (Roholm and Iversen[12]; Krarup and Roholm[13]) have expressed the belief that their liver biopsy specimens had shown a gradual transition from acute hepatitis to fully developed Laennec's cirrhosis. Dible and co-workers[14] concluded that "classical cirrhosis" may follow prolonged infectious hepatitis. Neefe[10] noted a mild, persistent inflammatory process in 2 specimens of liver taken six and nine months after the onset of induced viral hepatitis. He

3. Soffer, L. J., and Paulson, M.: Residual Hepatic Damage in Catarrhal Jaundice as Determined by the Bilirubin Excretion Test, Arch. Int. Med. **53**:809-813 (June) 1934.

4. Altschule, M. D., and Gilligan, D. R.: Chronic Latent Hepatitis Following Catarrhal Jaundice, New England J. Med. **231**:315-317 (Aug. 31) 1944.

5. Pratt, J. H., and Stengel, A.: Toxic Cirrhosis Resulting from Acute Liver Atrophy, Am. J. M. Sc. **173**:1-11 (Jan.) 1927.

6. Bloomfield, A. L.: The Natural History of Chronic Hepatitis (Cirrhosis of the Liver), Am. J. M. Sc. **195**:429-444 (April) 1938.

7. Barker, M. H.; Capps, R. B., and Allen, F. W.: Chronic Hepatitis in the Mediterranean Theater: A New Clinical Syndrome, J. A. M. A. **129**:653-659 (Nov. 3) 1945.

8. Fox, J. P.; Manso, C.; Penna, H. A., and Para, M.: Observations on the Occurrence of Icterus in Brazil Following Vaccination Against Yellow Fever, Am. J. Hyg. **36**:68-116 (July) 1942.

9. Klatskin, G., and Rappaport, E. M.: Late Residuals in Presumably Cured Acute Infectious Hepatitis, Ann. Int. Med. **26**:13-26 (Jan.) 1947.

10. Neefe, J. R.: Recent Advances in the Knowledge of "Virus Hepatitis," M. Clin. North America **30**:1407-1443 (Nov.) 1946.

11. Kelsall, A. R.; Stewart, A., and Witts, L. J.: Subacute and Chronic Hepatitis, Lancet **2**:195-198 (Aug. 9) 1947.

12. Roholm, K., and Iversen, P.: Changes in Liver in Acute Epidemic Hepatitis (Catarrhal Jaundice) Based on Thirty-Eight Aspiration Biopsies, Acta path. et microbiol. Scandinav. **16**:427-442, 1939.

13. Krarup, N. B., and Roholm, K.: The Development of Cirrhosis of the Liver After Acute Hepatitis, Elucidated by Aspiration Biopsy, Acta med. Scandinav. **108**:306-331, 1941.

14. Dible, J. H.; McMichael, J., and Sherlock, S. P. V.: Pathology of Acute Hepatitis: Aspiration Biopsy Studies of Epidemic, Arsenotherapy and Serum Jaundice, Lancet **2**:402-408 (Oct. 2) 1943.

did not mention fibrosis. Watson and Hoffbauer[15] have presented cases intended to show the transition from hepatitis to a type of cirrhosis which they considered similar to the so-called hypertrophic biliary cirrhosis of Hanot and for which they suggested the term "cholangiolitic cirrhosis." Fearnley[16] reported a case in which nodular hyperplasia of the liver clinically resembling portal cirrhosis followed infective hepatitis. Droller[17] mentioned 3 cases of cirrhosis subsequent to hepatitis. Steigmann and Popper[18] published 2 cases of hepatitis with protracted biliary obstruction in which autopsy showed cirrhosis. Axenfeld and Brass[19] concluded that in some instances of infectious hepatitis a transition leading to cirrhosis is observed. Klatskin and Rappaport[9] indicated that infectious hepatitis occasionally leads to "nodular cirrhosis" but rarely, if ever, to portal cirrhosis. T. B. Mallory[20] stated that he saw a number of cases of hepatitis in civilians followed by "toxic cirrhosis" as defined by F. B. Mallory.

Thus it is evident that infectious hepatitis in some cases leads to chronic injury of the liver. Two main questions arise from this conclusion: (1) What type of injury results? (2) Does the lesion represent a new entity or does it correspond to other forms of chronic hepatic injury?

REPORT OF CASES

CASE 1.—A 22 year old Negro woman was admitted to the hospital during the night of Sept. 8, 1946, and died early the next morning. She had had symptoms of a duodenal ulcer (roentgenographically demonstrated) for seven years. In 1941 she experienced hematemesis and melena, for which she was treated by transfusion. Eight months later she began to complain of weakness and easy fatigability and was found to be jaundiced and to have hyperproteinemia (10.7 Gm. per hundred cubic centimeters) and hyperglobulinemia. Reaction to the Frei test was negative. She had anemia (normochromic erythrocytes). Ability to excrete sulfobromophthalein sodium and hippuric acid was greatly impaired. After a few weeks the jaundice subsided, but the results of liver function tests remained abnormal. She

15. Watson, C. J., and Hoffbauer, F. W.: The Problem of Prolonged Hepatitis with Particular Reference to the Cholangiolitic Type and to the Development of Cholangiolitic Cirrhosis of the Liver, Ann. Int. Med. **25**:195-227 (Aug.) 1946.

16. Fearnley, G. R.: Ascites Following Infective Hepatitis, Lancet **1**:137-139 (Jan. 25) 1947.

17. Droller, H.: An Outbreak of Hepatitis in a Diabetic Clinic, Brit. M. J. **1**:623-625 (May 5) 1945.

18. Steigmann, F., and Popper, H.: Intrahepatic Obstructive Jaundice, Gastroenterology **1**:645-654 (July) 1943.

19. Axenfeld, H., and Brass, K.: Klinische und bioptische Untersuchungen über den sogenannten Icterus catarrhalis, Frankfurt. Ztschr. f. Path. **57**:147-236, 1942.

20. Mallory, T. B., in discussion on papers of Weir, Osgood, Giansiracusa, Althausen, Capps, Sborov, Barker, Wilbur, Havens, Mallory, Kimball, Chapple and Sones, Hoffbauer, Boles, Crew and Dunbar and Morrison, J. A. M. A. **134**: 678 (June 21) 1947.

was discharged with a diagnosis of questionable subacute yellow atrophy; cirrhosis, however, was being considered. She was readmitted in March 1943. At that time she was again jaundiced; the liver was slightly enlarged, with a firm, smooth, nontender edge. The level of the total serum proteins was normal, but the globulin was slightly increased. The cephalin-cholesterol flocculation test showed a 4 plus reaction. There was impaired excretion of hippuric acid. The gallbladder was normal. Her diet had been good, and there was no evidence of alcoholism. She had remained asymptomatic until two days before the last admission, when epigastric pain began, and she passed five tarry stools. She became nauseated, vomiting clear yellow fluid, only the last of which was blood tinged. The next day she became comatose and was admitted to the hospital.

She was a well developed young Negress, in a semicomatose state. Her skin was warm and only slightly moist. The eyeballs were slightly jaundiced. The lungs were clear, and the heart, except for tachycardia (120 to 150 beats per minute), was normal. The blood pressure was 130 systolic and 60 diastolic. No abdominal tenderness could be elicited, nor could organs be felt. The liver dulness was 6 cm. in extent in the right midclavicular line. Rectal examination revealed traces of a tarry appearance, and a guaiac test indicated presence of blood.

The urine was normal, except for mild pyuria, with a specific gravity of 1.008, but tests for bile and urobilinogen were not made. There were 2,900,000 red cells per cubic millimeter of blood, with 7.1 Gm. of hemoglobin per hundred cubic centimeters of blood: there were 18,000 leukocytes per cubic millimeter, with a normal differential count. The blood nonprotein nitrogen was 51 mg. per hundred cubic centimeters. The spinal fluid was normal.

The coma deepened, and the patient died twelve hours after admission. No hemodilution had occurred, and it was thought that her gastrointestinal bleeding had stopped or at least diminished greatly.

Autopsy.—Gross Examination: The scleras were slightly icteric. No ascites was present. The liver weighed 900 Gm. Its surface was diffusely nodular. The nodules ranged from about 2 to 10 mm. in size and were yellowish tan. The intervening tissue was somewhat wrinkled and reddish gray. The consistency of the liver was increased. The cut surfaces showed similar nodules, and the lobular pattern had completely disappeared. The gallbladder and the bile ducts were normal. The spleen weighed 280 Gm. and was of normal consistency. The malpighian corpuscles were indistinct, but the trabeculae were prominent. The esophageal veins were distended, and a small esophageal erosion, 2 by 4 mm., was found near the cardia. The stomach contained about 400 cc. of tarry material that gave a reaction for blood when the guaiac test was applied. Large amounts of similar material were present in the small and large intestines. In the first portion of the duodenum an area of old scarring was seen to involve all layers of the wall. The overlying mucosa appeared thin but intact. Areas of atelectasis were present in the lower lobes of both lungs. The combined weight of the kidneys was 370 Gm., and the organs were not grossly remarkable.

Microscopic Exmination: The liver cells formed small and large nodules, which were sometimes confluent. Large areas were completely devoid of liver cells and consisted only of the stroma with bile ducts. The nodules of parenchyma lacked the normal lobular pattern, although the attempt to reproduce the radial distribution of the liver cells around the efferent vein was generally quite obvious.

The intercellular relationship of the liver cells varied. Distinct cords were seen at the periphery, but these were unusually wide and displayed a prominent central cleft. Instead of a parallel arrangement, these cords tended to branch and

anastomose. A definite arrangement of the cells was lacking in the midzonal and central portion.

The liver cells varied somewhat in size, were generally large and occasional ones contained two or three nuclei. Small syncytial masses of cells without distinct cell contours occurred. The cytoplasm was finely granular and rather basophilic. Occasional large nuclei were present, some of which contained a single large vacuole.

Degenerative changes ranging from fatty metamorphosis to necrosis were often observed in the liver cells of the midzonal and central areas. Some liver cells showed hyaline cytoplasmic degeneration. These regressive changes were gradual, and even in necrotic areas the ghostlike outlines of the affected liver cells remained visible. The peripheral zones were rarely involved. Some budding and rare mitotic activity of the peripheral liver cells attested to regeneration.

The bile canaliculi were prominent and often contained small bile plugs.

The sinusoids were, in general, not remarkable. Where degenerative changes occurred in the parenchyma, the Kupffer cells proliferated and phagocytosed cellular debris. Polymorphonuclear leukocytes infiltrated these areas to a variable degree.

The reticulum stroma in the nodules was not remarkable. In the areas devoid of parenchyma the reticulum framework was collapsed and the individual fibers appeared thickened, but there was no evidence of new formation. The reticulum framework in these areas showed the normal arrangement of parallel and cross fibers, thus outlining clearly the collapsed lobules from which the liver cells had disappeared.

The portal spaces throughout showed condensation of their reticulum and connective tissue stroma, but there was no evidence of fibroblastic proliferation.

An inflammatory cell infiltration of slight to fair intensity was seen in the portal areas. The infiltrating cells were chiefly lymphocytes and plasma cells with a moderate number of large mononuclear cells. Some of these contained small amounts of brown pigment. Polymorphonuclear leukocytes were lacking except where fairly extensive degeneration was taking place in the adjacent parenchyma.

The large bile ducts were not remarkable. The number of small perilobular bile ducts was increased, but these showed no active proliferation. Rarely these small ducts contained bile casts. Often a direct continuity could be seen between the perilobular bile ducts and groups or cords of liver cells.

The branches of the hepatic artery and the portal vein were not remarkable. The large efferent veins occasionally suggested slight fibrosis of their walls.

The spleen showed marked depletion of lymphoid tissue and diffuse fibrosis of the stroma.

In the esophagus the veins of the submucosa were widely dilated.

The duodenum displayed extensive old scarring involving all layers of the wall. A small active ulcer, extending into the submucosa, was present, but there was no evidence of hemorrhage.

In the lungs aspiration pneumonia and atelectasis were observed.

The kidneys showed some subacute and chronic pyelonephritis.

Diagnosis.—Cirrhosis of the liver, posthepatitic; icterus; fibrosis of the spleen (280 Gm.); esophageal varices with erosion; hemorrhage, massive, into the gastrointestinal tract; duodenal ulcer, active, old; aspiration pneumonia; pulmonary atelectasis, and pyelonehritis, subacute and chronic were diagnosed.

CASE 2.—A 48 year old white carpenter was admitted to the hospital in October 1946. He complained of weakness of two to three years' duration and swelling

of the abdomen of three months, partly relieved by mercurial diuretics. He also had mild edema of the ankles, exertional dyspnea and moderate crampy pains in the upper abdominal region. For three years during the 1920's he had "drunk heavily"; he had stopped for a long time only to recommence five months before admission. His diet was always protein poor. The past history was unreliable; no account of previous jaundice or ascites was obtained.

He looked undernourished and slightly jaundiced. Three spider form telangiectases were seen on the anterior wall of his chest. There were basal rales in both lungs. The blood pressure was 150 systolic and 80 diastolic. The heart was normal. The abdomen was distended with fluid.

The urine had a specific gravity of 1.020 and contained bile, many erythrocytes, pus cells and a few granular casts. The patient was moderately anemic; his sedimentation rate (Westergren) was 110 mm. per hour. The white blood cells on admission numbered 4,350, with polymorphonuclears 67 per cent, "stab" forms 3 per cent, eosinophils 7 per cent, lymphocytes 22 per cent and monocytes 1 per cent. Serum proteins totaled 7 Gm. per hundred cubic centimeters of blood. The formaldehyde-gel test showed a positive reaction. The cephalin-cholesterol flocculation test was strongly positive on repeated occasions. The thymol turbidity test of the plasma was positive (33 units). The icterus index was 35. On admission there was no evidence of a tendency to bleed, but on the day of death (thirty-five days later) the clotting time (Duke method) was 12 minutes and the prothrombin time was 67 seconds—control, 32 seconds. The ascitic fluid was typical of a transudate. A roentgenogram of the upright abdomen was interpreted as showing nodularity of the liver.

The patient rapidly declined. His temperature, on admission 99.2 F., fluctuated daily between normal and 99.5 F. In his last week of life the jaundice intensified slightly and he became deeply comatose. His temperature dropped precipitously, and a day later he died.

Autopsy.—Gross Examination: The skin, the scleras and the conjunctivas were slightly icteric. The peritoneal cavity contained about 500 cc. of clear, yellowish green fluid. The liver weighed 1,350 Gm., and its surface was irregularly nodular. The nodules varied from 2 to 12 mm. in size and were generally yellowish tan and firm. Occasional nodules were either reddish brown or grayish yellow and soft. The tissue between the nodules was reddish and shrunken. The left lobe of the liver was atrophic and consisted merely of a thin lingula of reddish shrunken tissue with several nodules. The cut surfaces revealed similar nodules and complete loss of the lobular structure. The gallbladder was edematous but was otherwise not remarkable. The spleen weighed 560 Gm. and was firm. The malpighian corpuscles were indistinct, but the trabeculations were prominent. The esophagus showed dilation of the veins and several 1 to 2 mm. erosions, without evidence of hemorrhage. The duodenum and the proximal part of the ileum displayed edema. The mucosa of the distal part of the ileum was dark red and showed a few 1 to 2 mm. ulcerations. The mucosa of the colon was dark red in some areas. The small and large intestines contained large amounts of thick red fluid, which gave a positive reaction in the guaiac test. The combined weight of the kidneys was 435 Gm. The surfaces were finely and diffusely granular. The tips of the calices contained numerous tiny yellowish concretions. A small yellow granular stone was found in the left ureter where this passed through the wall of the bladder. The lungs showed atelectasis in both lower lobes. The bronchi contained much thick greenish mucus. Generalized arteriosclerosis was fairly marked.

Microscopic Examination: The liver showed complete loss of the lobular structure, with small nodules of parenchyma separated by varying-sized bands of stroma. Large areas were completely devoid of liver cells.

Peripherally in the nodules the liver cells tended to form wide, anastomosing cords, which on cross section were tubules with prominent central lumens. Toward the centers of the nodules the liver cells were haphazardly distributed.

The liver cells were larger than usual, and some contained two or three nuclei. The rather basophilic cytoplasm was finely granular. Rarely nuclei were vacuolated. In many nodules extensive degeneration of liver cells was seen, which involved chiefly the central and midzonal portions but often reached the periphery. Liver cells in varying stages of necrosis were seen. The contours of the necrotic cells could be discerned even in the most affected areas. There was little fatty metamorphosis and no hyaline degeneration. The uninvolved peripheral cells showed some regeneration.

The prominent bile canaliculi contained occasional bile casts.

The sinusoids in the necrotic areas were congested. Here hemorrhages and some infiltrations of polymorphonuclear leukocytes and rare large mononuclear cells were found. Elsewhere the sinusoids were not remarkable.

In the areas devoid of parenchyma the reticulum stroma was collapsed but showed the normal arrangement of parallel and cross fibers. The fibers appeared thickened, but there was no evidence of new formation of either reticulum or collagenous stroma. A similar condensation of the stroma without fibroblastic proliferation was seen in the portal spaces.

The portal spaces, as well as the areas depleted of parenchyma, showed some diffuse chronic lymphocytic and plasma cell infiltration. Polymorphonuclear leukocytes were present only in small numbers, except in areas adjacent to degenerating parenchymal nodules, where they were more numerous.

The small perilobular bile ducts were prominent, more numerous than usual and occasionally suggestive of proliferation. Some contained bile casts. These small bile ducts delineated the lobular contours in the areas from which the liver cells had disappeared. A direct continuity could be seen between these ducts and regenerated liver cells where these structures were found to abut. The larger bile ducts and the blood vessels were not remarkable.

The spleen displayed marked depletion of lymphoid tissue, congestion, and slight fibrosis of the stroma. The arteries and arterioles were sclerotic.

The esophageal and cardial veins were dilated and congested.

The small intestine showed edema of the submucosa, with a moderate acute inflammatory cell infiltration. A small recent erosion was seen at the tip of a mucosal fold. The submucosal veins were dilated.

The large intestine also showed submucosal edema and congestion. Numerous small recent hemorrhages were present in the mucosa, which was ulcerated in these areas.

The kidneys displayed marked swelling of the tubular epithelium and some arteriosclerosis.

In the lungs marked atelectasis and congestion were found. The bronchi contained much mucus.

Diagnosis.—Cirrhosis of the liver, posthepatitic; icterus; fibrosis of the spleen (560 Gm.); esophageal varices with erosions; phlegmonous enteritis, slight; edema and erosions of the colon; intestinal hemorrhage; ascites (500 cc.); tubular nephrosis, mild; nephrolithiasis, bilateral; ureterolithiasis, left; pulmonary atelectasis and congestion, and generalized arteriosclerosis and arteriolosclerosis were diagnosed.

CASE 3.—A 53 year old white bricklayer was hospitalized in January 1947, complaining of abdominal swelling of two or three months' duration. In 1942 he was hospitalized because of an episode of jaundice and ascites. At that time his liver was enlarged, the icterus index was 17 and there was 1.8 mg. of bilirubin per hundred cubic centimeters of blood. A flat roentgenogram of the abdomen taken some three months after the onset of jaundice showed a nodular liver. The patient left against advice and was apparently well and on an adequate diet, but he continued to drink alcoholic beverages to excess, as he had done for many years. In November 1946, his abdomen again started to swell, his scleras became yellow, his urine dark and his stools light. Because of these signs, he was hospitalized.

He appeared chronically ill and was slightly jaundiced. The lungs were clear, and the heart was normal. The blood pressure was 120 systolic and 70 diastolic. The abdomen was markedly distended with fluid, and there was slight pitting pretibial edema.

The urine contained bile and urobilinogen in a dilution of 1:20 on admission, later in a dilution of 1:80. There was slight anemia (red cells hyperchromic). The sedimentation rate (Westergren) was 82 mm. in one hour. The white blood cells were normal. The serum proteins totaled 5.0 Gm. per hundred cubic centimeters, and the formaldehyde-gel test showed a positive reaction. The cephalin-cholesterol flocculation test showed a strongly positive result on repeated occasions, and the thymol turbidity test of the plasma was twice positive (32 and 38 units). The prothrombin time was normal on several occasions. The ascitic and pleural fluid (formed after admission) had the character of a transudate. Abdominal venography showed an unobstructed inferior vena cava.

The patient's course was steadily downhill. His only complaint was anorexia. His temperature, normal on admission, fluctuated from normal to 101 F. during the last week. Ascitic fluid formed as rapidly as it was removed. Vigorous attempts to supply his needs by oral and intravenous administration of protein failed. Evidence of phlebothrombosis appeared in the legs; ligation of both superficial femoral veins was done. The patient died in coma shortly thereafter, on the thirty-fourth day of hospitalization.

Autopsy.—Gross Examination: The scleras were slightly icteric. The peritoneal cavity contained about 3,000 cc. of dark amber fluid. The liver weighed 1,080 Gm. Its surface was studded with firm, yellowish tan nodules, varying from 1 to 15 mm. in size, between which small and larger areas of shrunken, reddish gray tissue were present. On the cut surface the centers of some nodules were gray or red. The intervening shrunken tissue showed complete loss of lobular structure. The gallbladder was edematous. The spleen weighed 570 Gm. and was firm. Its cut surface was dark red, with prominent trabeculae. The esophageal veins were dilated, and the cardial mucosa showed two small areas of hemorrhage. Segments of the small and large intestines were edematous, but not otherwise remarkable. The combined weight of the kidneys was 455 Gm. On their cut surface the cortex was swollen, with some disappearance of landmarks. The left pleural space was largely obliterated by dense fibrous adhesions, but contained 1,100 cc. of amber fluid. About 500 cc. of similar fluid was found in the right pleural cavity. A recent infarct was present in the lower lobe of the left lung. The upper lobe of this lung and the lower lobe of the right lung showed atelectasis. Each groin showed the site of a recent ligation of the superficial femoral vein. A thrombus was found in the right femoral vein above the ligation. Dependent edema was present, more marked in the right leg and thigh. There was mild generalized arteriosclerosis.

Microscopic Examination: The liver had lost its lobular structure, and the liver cells formed small and large nodules separated by varying-sized bands or areas which were completely devoid of parenchyma.

In the nodules the liver cells showed generally a haphazard arrangement, with only slight tendency to aline in cords at the periphery.

The liver cells were larger than usual and sometimes displayed two or three nuclei but did not form syncytia. The quite basophilic cytoplasm was finely granular.

Degenerative changes were prominent in many nodules, where they were seen chiefly in the central and midzonal areas. There was extensive fatty metamorphosis, which occasionally had progressed to complete necrosis. The necrotic cells, however, persisted in the involved areas, where their outlines could be discerned. The unaffected cells showed some regeneration.

Bile casts were encountered in occasional canaliculi, which were always prominent. These casts were best seen in the central clefts of liver cell cords in cross section.

The prominent congested sinusoids were generally not remarkable except in areas of necrosis, where they were disrupted. Recent hemorrhage with slight filtration of polymorphonuclear leukocytes and large mononuclear cells was seen in most areas of necrosis.

The reticulum stroma of the nodules was not remarkable. In the areas depleted of parenchyma the stroma preserved the lobular pattern without appreciable new formation of either reticulum or collagen. The stroma appeared condensed, with thickening of the individual fibers.

Similarly, the portal spaces failed to show any fibroblastic proliferation but displayed some chronic inflammatory cell infiltration (lymphocytes, plasma cells and rare large mononuclear cells).

The small perilobular bile ducts were numerous and often connected with regenerated liver cells. Rarely these ducts contained bile casts.

The larger bile ducts, as well as the blood vessels and lymphatic channels, were not remarkable.

The spleen showed marked depletion of lymphoid tissue and congestion, with fibrosis of the stroma.

The cardial mucosa was ulcerated and showed an acute inflammatory cell infiltration. The submucosal veins were dilated.

Sections of small and large intestine revealed marked edema of the submucosa with diffuse acute inflammatory cell infiltration, which also involved the other layers.

The kidneys displayed swelling of the tubular epithelium.

In the lungs considerable chronic passive congestion and atelectasis were seen. One section showed part of a recent infarct.

Diagnosis.—Cirrhosis of the liver, posthepatitic; icterus; fibrosis of the spleen (570 Gm.); esophageal varices with erosions; phlegmonous enterocolitis; ascites (3,000 cc.); edema, dependent; ligation of both superficial femoral veins postoperative, recent; thrombosis of the right femoral vein; pulmonary infarction; pulmonary congestion, marked; pulmonary atelectasis; hydrothorax (right, 500 cc.; left, 1,100 cc.); pleural adhesions, fibrous, of the left side; tubular nephritis, slight, and generalized arteriosclerosis, mild, were diagnosed.

Case 4.—A 64 year old white carpenter was admitted April 16, 1947 and died forty hours later.

His last illness began about the first of January 1947, when he experienced a sudden onset of nausea and vomited large amounts of bloody material. He had

melena for five to six days. A few days after the onset his abdomen began to swell for the first time, and his feet began to swell shortly thereafter.

The past history revealed that there had been moderate, but persistent, intake of alcoholic liquors ever since boyhood. He had always eaten well. Fifteen years previously he had jaundice and general malaise for about five weeks, after which he felt completely well until 1947.

With the aforementioned complaints he was hospitalized on Jan. 14, 1947, at which time physical examination revealed an afebrile, nonjaundiced man whose only abnormalities were ascites, enlargement of the spleen and moderate edema of the lower extremities.

The Kahn test of the blood was positive. The sedimentation rate (Westergren) was 109 mm. in one hour. He had a normocytic anemia, 1.2 per cent reticulocytes, 883,000 platelets and 3,100 white blood cells per cubic millimeter of blood on admission. The differential count was normal. The total white cell count varied from 2,100 to 3,100 during his hospital stay. The blood nonprotein nitrogen was normal. Serum proteins on admission totaled 6 Gm. per hundred cubic centimeters; this value rose to 7 Gm. The formaldehyde-gel test showed a positive reaction at all times (6 estimations). The cephalin-cholesterol flocculation test was persistently positive. The thymol turbidity test was twice positive (38 and 32 units). A test with sulfobromophthalein sodium (5 mg. per kilogram of body weight) showed 40 per cent retention after thirty minutes (the icterus index at this time was normal). The icterus index, which on admission was 15, had dropped to 5 at the time of discharge. The stool contained bile. The ascitic fluid had the character of a transudate. The bleeding, clotting and prothrombin times were normal. Swallowed barium sulfate revealed marked esophageal varicosities. A hippuric acid excretion test done five days before discharge produced 1.35 Gm. of hippuric acid (1.77 Gm. of sodium benzoate was given intravenously).

During a hospital stay of two months the patient improved markedly on a regimen which included a high protein diet with supplementary vitamins and choline, resting in bed, paracenteses, and the administration of mercurial diuretics. He was discharged on March 12, 1947, to regain strength. The plan was to readmit him to the surgical service for treatment of his esophageal varices.

During the interim the ascitic fluid collected fairly rapidly, but otherwise the patient felt well. On April 16, however, he vomited bright red blood, had a tarry bowel movement and became irrational. The next day he was readmitted to the hospital. At this time he was in shock. The temperature was normal, the pulse rate was 144 and the blood pressure was 80 systolic and 60 diastolic. There was no visible jaundice. The mucous membranes were pale. The lungs were clear and resonant. Marked ascites was present. The edge of the liver (felt after paracentesis) was hard and extended 3 cm. below the rib margin in the midline. Tarry feces were present in the rectum and gave a positive reaction in the guaiac test. There was no peripheral edema.

The urine was normal except for 2 to 5 hyaline casts per high power field. A Kahn test of the blood was negative. There were 2,560,000 red cells per cubic millimeter of blood and 6.8 Gm. of hemoglobin per hundred cubic centimeters of blood. The hematocrit reading was 22. The sedimentation rate was 17 mm. in one hour. There were 8,150 white cells per cubic millimeter, with a normal differential count.

The patient was given sedative treatment and two transfusions of 500 cc. of whole blood, but the shock persisted. About twenty-four hours after admission he vomited 150 cc. of dark red blood. He died in coma forty hours after admission.

Autospy.—Gross Examination: The peritoneal cavity contained 1,800 cc. of cloudy amber fluid. The liver weighed 1,520 Gm., and its surface was irregularly

nodular. The nodules were yellowish tan or reddish brown and firm and varied from 1 to 20 mm. in size. Between the nodules were varying-sized areas of shrunken, reddish gray tissue which lacked any trace of lobular pattern. The right lobe of the liver contained near its diaphragmatic surface a 3 cm. cyst filled with dark brown granular material. The cut surfaces revealed complete loss of lobular structure and presence of nodules of the already described appearance set against a background of shrunken parenchyma. The portal and hepatic veins were not remarkable. The gallbladder and the bile ducts were normal. The spleen weighed 650 Gm., was firm and displayed a uniformly dark red cut surface. The esophageal veins were distended. The stomach and the intestines contained large amounts of thick reddish material, which gave a positive reaction in the guaiac test. Segments of the small and large intestines were edematous. The combined weight of the kidneys was 330 Gm. Each pleural cavity contained about 200 cc. of fluid. Areas of bronchopneumonia were noted in both lungs. The aorta, as well as the larger arteries, showed marked arteriosclerosis. Permission to examine the central nervous system was not granted.

Microscopic Examination: The liver showed complete loss of lobular structure. Small and large nodules of haphazardly arranged liver cells were separated by bands or wide areas which were devoid of parenchyma. The liver cells were larger than normal; sometimes they were multinucleated and occasionally they formed syncytia. The intercellular bile canaliculi were prominent but did not contain bile casts.

Except for patchy areas of fatty metamorphosis occurring chiefly in the central and midzonal portions of the nodules, no degenerative changes were noted.

A number of nodules in sections taken from widely separated portions of the liver were composed of neoplastic cells, which, however, closely reproduced the structure and the cytologic characteristics of liver cells. The tumor cells were arranged in abortive columns and cords, which commonly displayed a central cleft or channel. Between the cells intercellular bile canaliculi might be seen, which sometimes contained definite bile casts. The cells and their nuclei displayed definite pleomorphism and frequently formed syncytial masses. The round or oval nuclei were large and vesicular, with generally one prominent nucleolus, which was eccentrically placed near the nuclear membrane. Rare mitoses were present. The cytoplasm was ample, granular and markedly basophilic. Many cells displayed multiple fat droplets, which did not displace the nuclei. In addition, many tumor cells exhibited in their cytoplasm prominent dense acidophilic masses of round or oval shape. Hemorrhage and necrosis of the neoplastic tissue were observed only in the sections of the cystic area described. Invasion of larger blood vessels by tumor was not observed, but small groups of neoplastic cells were commonly present around the larger tumor nodules.

The tumor masses possessed a well formed reticulum framework and a rich sinusoidal blood supply, both of which were quite similar to those of the non-neoplastic nodules of the liver.

The large tumor nodules were surrounded in a capsule-like fashion by condensed hepatic stroma, which displayed some proliferation of connective tissue. Many of the smaller neoplastic masses lacked capsules but compressed the surrounding liver cells.

Away from the neoplastic masses the stroma in the often quite extensive areas devoid of parenchyma was condensed, with thickening of the fibers, but the stromal structure of the original collapsed hepatic lobules persisted without new formation of either reticulum or collagen. The portal spaces showed no scarring and were infiltrated by small numbers of lymphocytes and plasma cells.

The small perilobular bile ducts were increased in number and were often seen to connect with the liver cells. The larger bile ducts were not abnormal.

The sinusoids of the hepatic nodules, as well as the larger blood vessels and the lymphatic channels, were not remarkable.

The spleen showed fibrosis of the stroma, congestion, and depletion of lymphoid tissue.

The cardiac veins were widely dilated. Sections of the small and the large intestine showed edema of the submucosa with diffuse acute inflammatory cell infiltration, which also involved other layers.

The kidneys revealed some arteriosclerosis.

The lungs showed bronchopneumonia, edema and congestion. No tumor metastases were found.

Diagnosis.—Cirrhosis of the liver, posthepatitic; hepatocellular carcinoma of the liver; fibrosis of the spleen (650 Gm.); esophageal varices; hemorrhage in the gastrointestinal tract; phlegmonous enterocolitis; ascites (1,800 cc.); bilateral hydrothorax (200 cc.); bronchopneumonia; pulmonary edema, and generalized arteriosclerosis were diagnosed.

CASE 5.—A 53 year old Negro laborer who suffered from chronic alcoholism and gave a poor dietary history was admitted on June 6 and died on June 19, 1947.

In 1937 he was hospitalized for a month because of intermittent epigastric pain, sense of fulness and nausea of one year's duration. He was jaundiced and had ascites, and the liver was enlarged and tender. The icterus index was 80. The urine contained bile and urobilinogen. A Wassermann test of the blood was negative. The sedimentation rate was 19 mm. in one hour. He improved gradually and went back to work, although he never felt completely well again.

In 1944, when he was admitted because of myocardial infarction, the liver was felt 2 to 3 fingerbreadths below the costal margin. He was not anemic. No studies of liver function were made.

In 1945 he again began to have nausea following ingestion of fatty foods. This persisted and in 1946 was accompanied by epigastric pain. In February 1947 he was rehospitalized. For two months preceding his admission he had aching in the right upper abdominal quadrant and abdominal swelling. At this time examination disclosed enlargement and tenderness of the liver, which was smooth and firm, moderate splenomegaly, mild edema of the ankles and evidence of hypertensive, arteriosclerotic cardiovascular disease. The red and white blood cell counts were normal. The sedimentation rate was 107 mm. in one hour. The urine contained urobilinogen (1:50). There was 40 per cent retention of sulfobromophthalein (test dose, 5 mg. per kilogram) at thirty minutes on two occasions. Serum proteins totaled 6 Gm. per hundred cubic centimeters on admission and 7.4 Gm. a month later; the formaldehyde-gel test showed a positive reaction both times. His icterus index was 13. The cephalin-cholesterol flocculation test was constantly positive, and the thymol turbidity test of the plasma was positive (23 units). The bleeding, clotting and prothrombin times were normal. Needle biopsy of the liver resulted in a diagnosis of posthepatitic cirrhosis. He had several bouts of unexplained fever lasting three and four days. Despite his resting in bed and adhering to a high protein diet with vitamin supplements and choline, he did not improve and was discharged after a two months' stay.

He existed at this level for about a month. Then his abdomen began to swell, and his weakness increased. This led to his final admission. At this time he was moderately jaundiced. A spider form angioma was noted on his left shoulder. There was right hydrothorax. The liver, which was palpable 3 fingerbreadths

below the costal margin, was hard and tender. There was moderate ascites, also edema of the ankles. During the previous four months he had become remarkably emaciated. The urine contained bile and urobilinogen. He had 13.5 Gm. of hemoglobin per hundred cubic centimeters and 7,000 white blood cells per cubic millimeter of blood, with a normal differential count. The sedimentation rate was 64 mm. in one hour. The icterus index was 22 on this admission; the cephalin-cholesterol flocculation test was positive. The thymol turbidity test of the plasma was positive (37 units). The serum proteins totaled 7 Gm. per hundred cubic centimeters. The formaldehyde-gel test was positive. The icterus index rose to 46 and then to 60 two days before death. On the day before death his prothrombin time was equal to that of a 20 per cent normal control. His course proceeded downhill. He had severe abdominal pain and bloody diarrhea lasting five days, became comatose, and died on the twelfth hospital day.

Autopsy.—Gross Examination: The scleras were icteric. The peritoneal cavity contained 300 cc. of clear amber fluid. The liver weighed 3,260 Gm. and was irregularly nodular. The hepatic nodules ranged from 3 to 15 mm. in size and were soft and yellowish brown. Between the nodules narrow or wide bands of shrunken, reddish gray tissue were present. The lateral and diaphragmatic aspect of the right lobe contained a large, soft mass. In this area the surface of the organ showed yellowish red nodules ranging from 20 to 50 mm. in size. The cut surfaces of this portion of the liver revealed a soft, greenish yellow, multinodular tumor mass, about 12 cm. across, which displayed several dark red areas of necrosis. The cut surfaces of the rest of the organ showed complete loss of normal structure with nodules of yellowish brown parenchyma against a background of varying-sized, often extensive areas of shrunken tissue. The hepatic veins, as well as a major branch of the portal vein, were invaded by tumor. The gallbladder and the bile ducts were not remarkable. The spleen weighed 470 Gm. and was firm. Its cut surfaces were deep reddish brown, with indistinct malpighian corpuscles and prominent trabeculae. No esophageal varices were found. The small and large intestines were edematous in areas, but there was no hemorrhage. Each pleural cavity contained about 100 cc. of clear fluid. The lungs were studded with many yellow, soft nodules ranging from 1 to 20 mm. in size. The combined weight of the kidneys was 235 Gm. On their cut surface the usual landmarks were indistinct. The heart weighed 330 Gm. and showed an area of old fibrosis, 10 by 20 mm. in diameter, in the interventricular septum just beneath the aortic ring. The coronary arteries were somewhat sclerosed. There was some generalized arteriosclerosis. The brain showed no metastases.

Microscopic Examination: The liver consisted of small and large nodules of parenchymal cells scattered in a background of stroma which in many areas was completely devoid of liver cells.

The liver cells were large, often multinucleated, and frequently formed syncytial masses. The intercellular bile canaliculi were prominent and often contained bile casts.

Many hepatic nodules displayed degenerative changes, which occurred mostly in the central and midzonal areas but sometimes involved the peripheral zones. The changes consisted chiefly of fatty metamorphosis, but areas of necrosis of liver cells were also present. The remnants of the necrotic cells persisted in the involved areas, where a slight to moderate concentration of neutrophilic polymorphonuclear leukocytes and some extravasation of red blood cells were seen. In these areas the Kupffer cells were prominent and displayed phagocytosis. The liver cells peripheral to the necrotic areas showed some regeneration.

Sections taken from the mass in the right lobe of the liver displayed nodules of neoplastic cells which, despite considerable anaplasia, closely resembled liver cells. The tumor cells tended to arrange themselves in bizarre columns, in which there were central clefts. Between the cells distinct intercellular bile canaliculi were often seen, and these frequently contained bile casts. The neoplastic cells were large, with ample cytoplasm which was granular and quite basophilic. The vesicular nuclei tended to be round or oval and frequently had multiple prominent nucleoli, which were placed eccentrically, near the nuclear membrane. Mitoses were frequent and sometimes atypical. Fat vacuoles were present in some tumor cells, and there were many areas of necrosis, accompanied by some hemorrhage and slightly infiltrated by neutrophilic polymorphonuclear leukocytes. Tumor invasion of blood vessels was noted in many instances. A well formed but delicate reticulum framework and an ample sinusoidal blood supply were observed in the tumor masses. The neoplastic cells freely invaded the surrounding tissue.

The tumor nodules, as well as the nodules of non-neoplastic liver cells, were set in a background of condensed hepatic stroma, which in many and often rather extensive areas was devoid of liver cells. The original lobular pattern of the stroma remained unaltered. The individual fibers appeared thickened, but there was no new formation of either reticulum or collagen in these areas. The portal spaces were approximated in consequence of the collapse of the liver lobules. They were infiltrated by small numbers of chronic inflammatory cells. Only near areas of necrosis might a slight concentration of neutrophilic polymorphonuclear leukocytes be found.

The small perilobular bile ducts were numerous and were often continuous with the liver cells at the peripheries of the non-neoplastic nodules. The large bile ducts were not remarkable.

The sinusoids were markedly congested. The large blood vessels and lymphatic channels were not remarkable except for occasional tumor invasion of the former.

The spleen showed fibrosis, congestion and depletion of lymphoid tissue.

The lungs displayed numerous metastatic tumor nodules identical with those found in the liver. The tumor cells were seen to produce bile in some instances. Small groups and large masses of neoplastic tissue were seen in many blood vessels. Some early bronchopneumonia was also present.

The cardial veins were somewhat dilated. The small and large intestines showed some edema of the submucosa.

The kidneys revealed swelling of the tubular epithelium as well as some arterial and arteriolosclerosis.

The heart showed small patchy areas of old fibrosis. Sections from the area in the interventricular septum described in the gross specimen showed complete replacement of the myocardium by dense connective tissue. The branches of the coronary artery were sclerotic.

Diagnosis: Cirrhosis of the liver, posthepatitic; hepatocellular carcinoma of the liver with pulmonary metastases; icterus; fibrosis of the spleen (470 Gm.); ascites (300 cc.); hydrothorax (100 cc. bilaterally); segmental edema of the intestines; myocardial infarction, healed; myocardial fibrosis; generalized sclerosis of arteries and arterioles; bronchopneumonia, and tubular nephritis, mild, were diagnosed.

COMMENT

The clinical picture in these cases was that of hepatic failure with portal hypertension. Icterus and ascites were present in all, ascites in 4, and severe gastrointestinal bleeding in 3. Laboratory findings indicative of hepatic failure were present in all. Although there was no doubt as to

the presence of hepatic failure, the pathologic basis of the process could not be determined by physical or laboratory findings.

The histories of 4 patients, however, suggested previous episodes of hepatitis. Hepatitis was observed to develop in the first patient eight months after a transfusion and five years before her final admission. The first episode of hepatitis was prolonged, and even after subsidence of jaundice, studies of liver function showed appreciable impairment. Another bout occurred a year later, at which time hepatic function was again shown to be poor. This history is consistent with post-transfusion hepatitis.[11] The third patient was seen in 1942 because of jaundice, ascites and evidence of severely impaired hepatic function. His clinical picture was compatible with severe hepatitis.[21] The long symptom-free interval makes it more likely that the preceding episode represented hepatitis rather than decompensated Laennec's cirrhosis. The past histories of the fourth and fifth patients are essentially similar, episodes consistent with hepatitis having occurred fifteen and ten years, respectively, before the condition progressed to fatal liver failure.

The second patient's history, on the other hand, reveals no evidence of previous hepatitis. His case is included because the autopsy revealed changes strinkingly similar to those noted in the other 4 patients. The other patients were observed in the Grady Memorial Hospital and its clinics for many years and gave no history of having been exposed to drugs or poisons. The second, third, fourth and fifth patients suffered from chronic alcoholism.

The livers of all the patients were strikingly similar in their morphologic aspects and differed even on gross examination from the liver characteristic of Laennec's cirrhosis.

The weights of the livers of the first 3 patients ranged from 900 to 1,350 Gm. The surfaces were studded with firm yellow-tan nodules varying in diameter from 1 to 20 mm. Some nodules were soft and gray or red. Between the nodules in areas often several centimeters in diameter the tissue was shrunken and reddish gray. In the second patient the left lobe of the liver was atrophic and consisted of shrunken, reddish tissues with a few nodules. The cut surfaces showed the nodules against a background of atrophic tissue. The lobular structure was completely lost.

The gross appearance of the liver of the fifth patient, which weighed 3,260 Gm., was complicated by a superimposed primary liver cell carcinoma, which invaded the hepatic veins as well as a main branch of the portal vein. In this case the neoplasm was readily recognized, but in the gross examination of the liver of the fourth patient, which weighed 1,520 Gm., the presence of a tumor was not suspected. Otherwise these 2 livers were identical in gross appearance with the others.

21. Soffer and Paulson.[8] Kelsall and others.[11] Fearnley.[16]

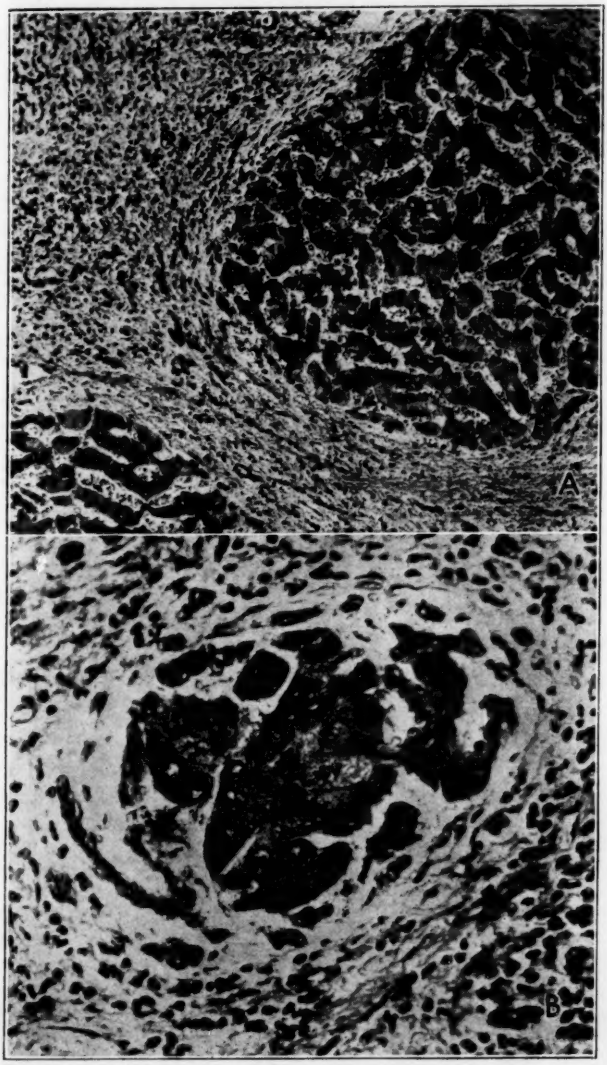

Fig. 1.—*A*, nodule of liver against a background of stroma devoid of liver cells; phloxine-methylene blue; × 105. The parenchymal cells form irregular, anastomosing cords. The intercellular bile canaliculi are prominent.

B, small nodule of regenerated liver cells surrounded by newly formed small bile ducts; phloxine-methylene blue; × 330.

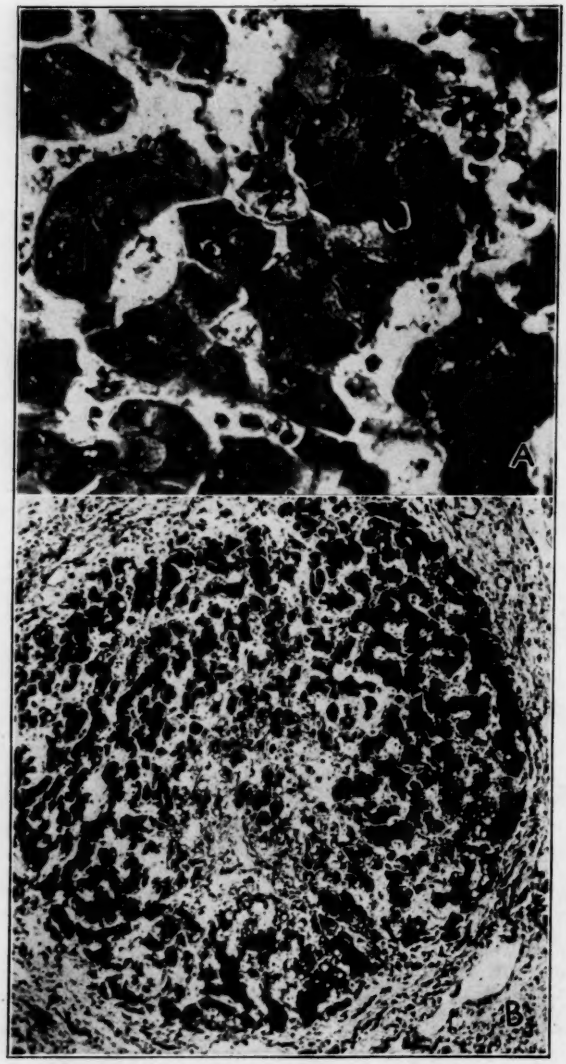

Fig. 2.—*A*, regenerated liver cells; phloxine-methylene blue; × 330. The intercellular bile canaliculi contain bile casts. The cross section of a liver cell cord at right of center shows the wide central cleft filled by large bile casts. A multinucleated liver cell is shown left of center.

B, degenerative changes in a liver nodule; phloxine-methylene blue; × 85. These changes occurred chiefly in the central and midzonal areas.

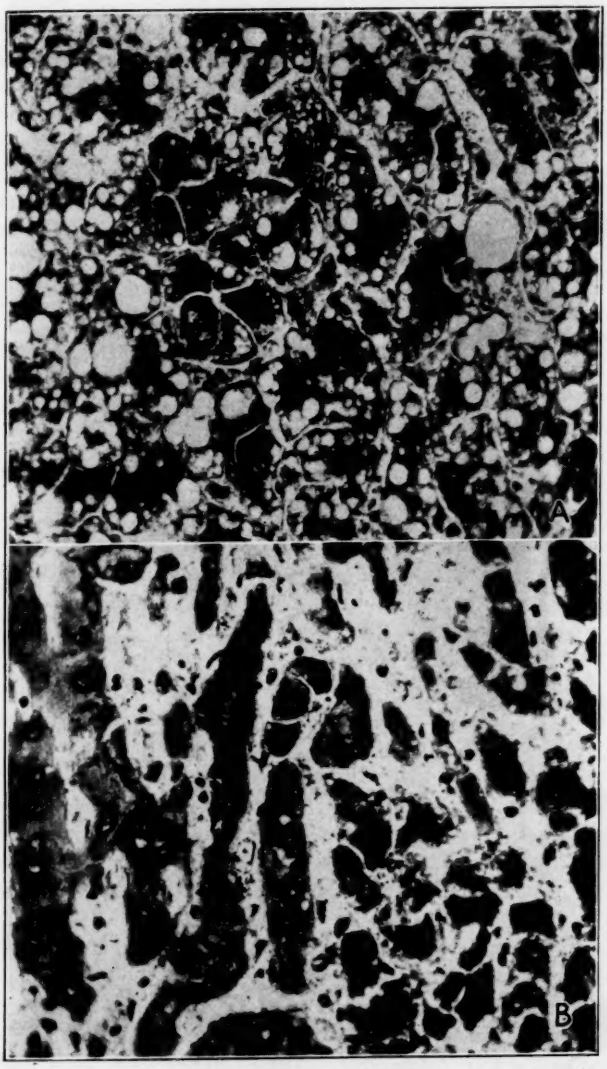

Fig. 3.—*A*, fatty metamorphosis of regenerated liver cells; phloxine-methylene blue; × 330.

B, varying stages of necrosis of regenerated liver cells; phloxine-methylene blue; × 330. The cells on the right side of the field are completely necrotic, but note that they persist.

Histologic examination showed small and large nodules of liver cells separated by bands and wide areas of stroma devoid of liver cells (fig. 1*A*). The nodules lacked a lobular pattern and were surrounded by many prominent small bile ducts (fig. 1*B*). The liver cells had obviously formed by regeneration. The cells varied in size, and multinucleated cells, as well as syncytial masses, were common. The intercellular bile canaliculi were prominent and often contained bile casts (fig. 2*A*). Degenerative changes of varying, often considerable, extent involved the liver cells (fig. 2*B*). They occurred chiefly in the centers and midzones of the nodules but sometimes extended to the peripheries. The changes ranged from fatty metamorphosis (fig. 3*A*) to necrosis, leaving behind the ghostlike outlines of the necrotic cells (fig. 3*B*). A mild infiltration of inflammatory cells (large mononuclear cells and polymorphonuclear leukocytes) accompanied these changes.

In the areas devoid of liver cells the stroma showed preservation of the lobular pattern (fig. 4*A*). The fibers were condensed and thickened, but the normal pattern of the stroma was unaltered (fig. 4*B*). No new formation of either reticulum or stroma could be observed. The contours of the collapsed liver lobules were delineated by the small perilobular bile ducts, which were increased in number and prominent (fig. 5*A*). The portal spaces showed no scarring, and there was only a mild degree of chronic inflammatory cell infiltration. The primary liver cell carcinoma observed in 2 cases presented a typical picture (fig. 5*B*). The tumor cells closely reproduced liver cells with intercellular bile canaliculi and actual formation of bile. The stroma of these tumors was a delicate reticulum framework with a rich sinusoidal blood supply. Pulmonary metastases were present in the fifth patient.

The findings in the other organs were those of portal hypertension and obstruction. Congestion and fibrosis of the spleen were noted in all patients, and esophageal varices were present in all but the fifth patient. Phlegmonous enterocolitis was observed in the second, third and fourth patients and segmental edema of the intestines in the first and fifth. Gastrointestinal hemorrhage had occurred in the first, second and fourth patients. In the first patient an old duodenal ulcer was present but was not the source of the hemorrhage.

Ascites was found in all but the first patient. Icterus was present in all but the fourth and appeared to result from obstruction of the small bile canaliculi within the parenchymatous nodules.

Our findings were quite similar to those described by Lucké in subacute infectious hepatitis. They differed from those of acute infectious hepatitis only in these points: The rapid death of liver cells and the

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22. Mallory, T. B.: The Pathology of Epidemic Hepatitis, J. A. M. A. **134**: 655-661 (June 21) 1947.

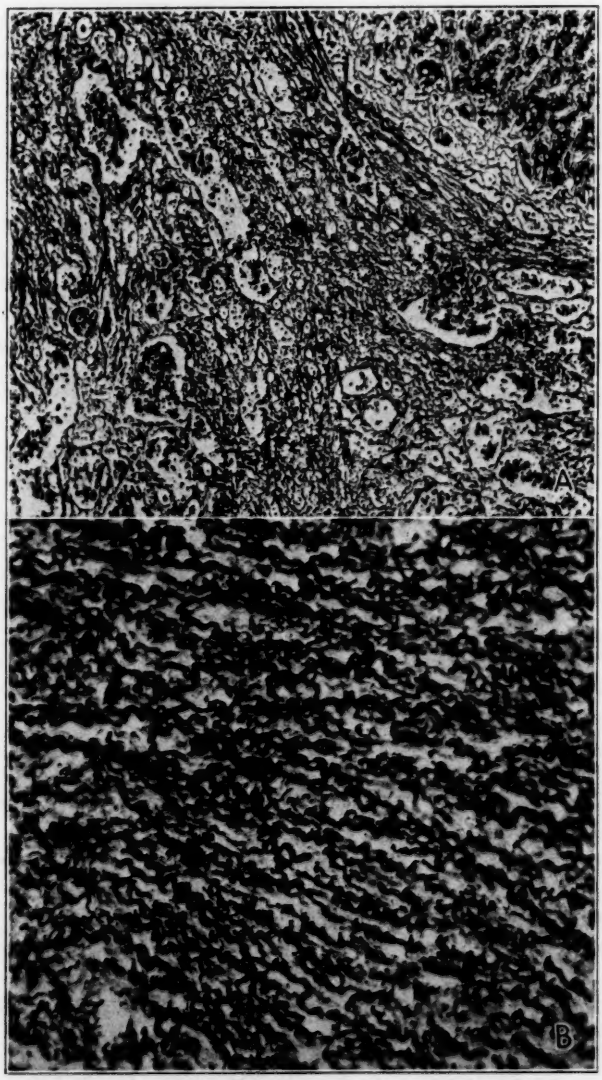

Fig. 4.—*A*, collapsed reticulum framework of an area devoid of parenchyma; Wilder's reticulum stain; × 80. A nodule of regenerated liver cells is shown in the right upper corner.

B, high power view of the reticulum stroma in an area devoid of parenchyma; Wilder's reticulum stain; × 365. The individual fibers are thickened, but the normal arrangement of parallel and oblique fibers is preserved.

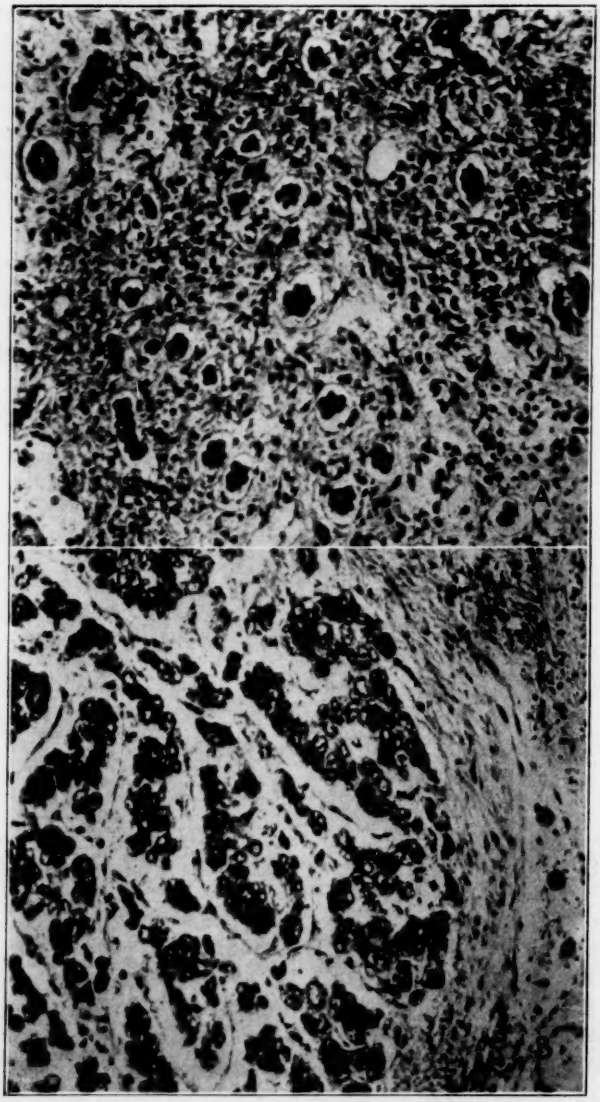

Fig. 5.—*A*, contours of the vanished hepatic lobules outlined by the numerous nowly formed small perilobular bile ducts; phloxine-methylene blue; × 160. There is no significant inflammatory cell infiltration.

B, primary liver cell carcinoma; phloxine-methylene blue; × 160. The neoplastic cells form cords and display a sinusoidal blood supply.

speedy removal of cellular debris which are characteristic of the acute stages of hepatitis seen at autopsy[22] were no longer present in our cases. By the same token, the inflammatory cell infiltration was chronic and not particularly active. On the other hand, degenerative changes were present in the regenerated liver cells in a varying but always appreciable degree. They could be traced through all phases from fatty metamorphosis to necrosis, and thereby the progressive character of the lesion was indicated. In Lucké's cases of subacute infectious hepatitis the liver displayed only a few areas of degeneration of this type and was said to show no evidence of progressive destruction of tissue.

Because of the active degenerative changes observed in our cases, we consider the lesion to have been progressive. The clinical course in our cases certainly agrees with this conclusion.

The mechanism of these degenerative changes is not understood. Lucké considered them probably secondary to ischemia and accumulation of metabolic products. One could also speculate that in liver cells which have regenerated in an infected organism a degree of adaptation has occurred between virus and host cells in some cases. Instead of rapidly dying, as in the fulminant form of the disease, or being completely restored on recovery as in most cases, the parenchymal cells may gradually degenerate in a few instances. The disease may then have a chronic progressive course. The resemblance observed between our findings and those of prolonged infectious hepatitis was striking. In fact, a chronic form of infectious hepatitis may account for this picture without the addition of secondary changes.

Our findings are not only similar to those described as occurring in infectious hepatitis, a disease termed in the past idiopathic acute yellow atrophy,[23] but they seem to us identical with those described by F. B. Mallory as seen in "toxic cirrhosis" in 1911[24a] and as "healed acute yellow atrophy" in 1932.[24b]

Karsner[25] preferred to call this lesion "post-necrotic cirrhosis" and stated that it follows various infectious diseases and injuries caused by certain poisons and drugs, as well as acute yellow atrophy. The latter is now known to be merely a designation of acute hepatic failure, whatever the cause.[26] Acute diffuse necrosis of liver cells, i.e., hepatitis, is

23. Case Records of the Massachusetts General Hospital, Case 28391, New England J. Med. **227**:485-487 (Sept. 24) 1942.

24. Mallory, F. B.: (*a*) Cirrhosis of the Liver: Five Different Types of Lesions from Which It May Arise, Bull. Johns Hopkins Hosp. **22**:69-75 (March) 1911; (*b*) Cirrhosis of the Liver, New England J. Med. **206**:1231-1239 (June 16) 1932.

25. Karsner, H. T.: Morphology and Pathogenesis of Hepatic Cirrhosis, Am. J. Clin. Path. **13**:569-606 (Nov.) 1943.

26. Acute Yellow Atrophy of the Liver, editorial, J. A. M. A. **133**:1156-1157 (April 12) 1947.

acknowledged to precede postnecrotic cirrhosis. The belief that bacterial toxins are involved in the production of this necrosis has been superseded by the recognition of a viral factor. Certain chemicals are known to produce this type of necrosis. We believe that in order to assign a chemical cause a definite history of exposure must be obtained. This is lacking in our cases.

Popper and Franklin[27] have recently stated that the morphologic picture of acute viral hepatitis differs from that of "toxic hepatitis." This interesting observation deserves further investigation, particularly with regard to possible differences in the progress and the end results of the tissue changes.

The lesion in our patients differed from other types of cirrhosis. The principal distinction was that the lobular pattern of the stroma had been preserved in the areas devoid of parenchyma without new formation of either reticulum or collagen. The varying-sized, often extensive areas of collapsed stroma separated islands of regenerated liver cells, which were irregularly distributed. The singular lack of stromal involvement has never been explained.

These features had been clearly defined by F. B. Mallory,[24] who stressed that the increase of the connective tissue in "toxic cirrhosis" was apparent rather than real. This he contrasted with other types of cirrhosis, particularly Laennec's, in which he emphasized the proliferation of fibroblasts resulting in actual increase of connective tissue.

F. B. Mallory[24] and Connor,[28] as well as Wilson and Goodpasture,[29] stated that the morphologic picture of "toxic cirrhosis" was sufficiently distinct to permit its identification. Karsner concluded that in typical cases "postnecrotic cirrhosis" may be easily recognized but doubted that this would be possible in borderline cases.

Cirrhosis of the liver has been recently defined[25] as a diffuse progressive chronic inflammation accompanied by fibrosis (i.e., new formation of connective tissue), retrogressive changes in the parenchyma and proliferation of remaining cells in the direction of regeneration. How, then, can we apply the term of cirrhosis to a hepatic lesion the diagnosis of which requires the absence of new formation of reticulum and collagen? In fact, we have speculated that this lesion may be nothing but an extremely protracted form of infectious hepatitis. The existing information about the natural history of infectious hepatitis invites such speculation, but present knowledge cannot confirm it.

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27. Popper, H., and Franklin, M.: Infectious Hepatitis Contrasted with Toxic Hepatitis, Proc. Inst. Med. Chicago **16**:353-354 (March 15) 1947.

28. Connor, C. L.: Toxic Cirrhosis of the Liver, Canad. M. A. J. **17**:546-551 (May) 1927.

29. Wilson, J. D., and Goodpasture, E. W.: Yellow Atrophy of the Liver, Acute, Subacute and Healed, Arch. Int. Med. **40**:377-385 (Sept.) 1927.

The term "cirrhosis" could be retained for the lesion we describe in conformity with the definition of F. B. Mallory, who applied the term to all sclerosed conditions of the liver, whether progressive or not, in which destruction of liver cells is associated with real or apparent increase of connective tissue. This definition does not require actual formation of connective tissue as an essential part of cirrhosis and is completely satisfied by the lesion we report. In fact, this lesion is identical with the "toxic cirrhosis" described by him.

In all our cases the clinical picture was consistent with that of Laennec's cirrhosis terminating either in hepatic failure or conditions associated with portal hypertension. However, we believe that all clinical data except those of biopsy of liver (which was diagnostic in the fifth case) are of uncertain value in differentiating long-standing infectious hepatitis from decompensated Laennec's cirrhosis. Therefore, we base our conclusions on morphologic findings. We think it probable that the hepatic lesion observed in our patients was the end result of infectious hepatitis. The problem of the end result of infectious hepatitis is now of special importance because of the size of the recent epidemics.

SUMMARY

Five patients were studied whose terminal illness was either hepatic insufficiency or a complication caused by portal obstruction. Three of these patients were studied repeatedly in the course of several years. In 3 patients the terminal clinical picture was identical with that of Laennec's cirrhosis, and in the other, with that of rapid hepatic failure.

Morphologic studies revealed a chronic progressive injury of the liver, complicated in 2 cases by superimposed primary liver cell carcinoma. The changes observed in our cases not only were identical with the lesion described in the past as toxic or postnecrotic cirrhosis or as healed acute yellow atrophy but bore a close resemblance to the changes in the subacute infectious hepatitis studied intensively in recent years. We suggest that the lesion which we enountered may be a chronic form of infectious hepatitis.

MASSIVE PICROTOXIN THERAPY IN TREATMENT OF ACUTE BARBITURATE POISONING

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THE PURPOSE of this presentation is to describe our experience in the treatment of acute barbiturate intoxication with massive doses of picrotoxin in 30 cases. These cases were seen since Jan 1, 1946.

The treatment of barbiturate poisoning has been extensively discussed in the literature with various therapeutic procedures recommended, depending on the drug of choice. We have selected 11 severe cases from our series to demonstrate the massive therapy employed. In 2 of the selected cases doses of picrotoxin greater than any previously recorded in the literature were given.[1]

It is usually difficult to determine the amount of barbiturate consumed and the time elapsed before hospitalization, so that the severity of the poisoning must be judged from the initial observations and the subsequent course. We considered intoxication to be severe: (1) when more than 1 to 2 Gm. of a barbiturate was ingested; (2) when unconsciousness prior to hospitalization was prolonged; (3) when coma was associated with absence of reflexes, and (4) when respiratory depression was present.

On the patient's admission to the hospital a rapid appraisal was made of his condition and depth of unconsciousness. This appraisal included principally a neurologic examination, determination of blood pressure and examination for signs of inadequate respiratory exchange, such as

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From Michael Reese Hospital.

1. Richards, R. K., and Menaker, J. G.: The Role of Picrotoxin in the Treatment of Acute Barbiturate Poisoning, Anesthesiology **3**:37-47 (Jan.) 1942. Boyd, E. M.: Picrotoxin for Barbiturate Poisoning, Canad. M. A. J. **54**:442-443 (May) 1946. Anderson, J. P.: Treatment of Barbiturate Intoxication, with Specific Reference to Picrotoxin: Report of Twenty Cases, Ann. Int. Med. **14**:2037-2046 (May) 1941. Billow, B. W.: Barbiturate Intoxication and Picrotoxin Treatment, J. Lab. & Clin. Med. **29**:263-269 (March) 1944. Dorsey, J. F.: The Picrotoxin Treatment of Barbiturate Poisoning, J. Nerv. & Ment. Dis. **99**:367-375 (April) 1944. Russo, J., and Nicholson, M.: The Treatment of Barbiturate Overdosage, Lahey Clin. Bull. **4**:246-251 (April) 1946. Burdick, D. L., and Rovenstine, E. A.: Picrotoxin in Barbiturate Poisoning, Ann. Int. Med. **22**:819-826 (June) 1945. Treatment of Barbiturate Poisoning, Conferences on Therapy, Am. J. Med. **1**:93-103 (July) 1946.

pharyngeal and tracheal obstruction or cyanosis. The immediate therapy was based on findings from these examinations. General supportive measures were instituted at once. Respiratory embarrassment and peripheral circulatory collapse were treated in the orthodox manner, i.e., with provision of an adequate airway (nasal or endotracheal), oxygen inhalations and intravenous administration of fluids. For several patients with respiratory depression the use of artificial respiration was necessary in conjunction with the administration of respiratory stimulants and analeptic drugs.

Gastric lavage was performed for most of these patients, in spite of the fact that they were unconscious many hours prior to admission. While the gastric tube was in place a saline cathartic was frequently administered. Samples of the gastric juice and urine were tested for barbiturates. If there was any doubt of the diagnosis, a spinal puncture was performed in an attempt to rule out any other intracranial pathologic condition, e.g., hemorrhage.

Frequent aspiration of mucus from the throat was continued as long as the patient was unconscious. The Trendelenburg position was often useful in preventing aspiration of secretions. Because of the high incidence of pulmonary complications, penicillin therapy was instituted for these patients from the time of their admission, even though they were afebrile and presented no signs of such a complication. Frequent turning of the patient in bed was also helpful in this regard.

Analeptic drugs are the vital part of therapy in severe barbiturate intoxications. Picrotoxin was used almost exclusively for our patients, although at times it was supplemented with "metrazol" desoxyephedrine hydrochloride and amphetamine. Goodman and Gilman[2] discussed the pharmacologic properties and modes of action of these drugs. In our series the method of administration was not unique, but much larger doses of analeptic substances were used than are ordinarily recommended in the literature. The individual dose of picrotoxin for these patients varied. Amounts ranging from 9 to 45 mg. per dose given intravenously at fifteen-minute intervals were necessary to obtain the desired degree of stimulation. Once intravenous administration of fluids was started, all medicaments were injected into the rubber tubing to save veins for future use and to avoid excessive trauma. As the patients improved, the amount of drug was progressively decreased, according to the irritable response obtained from the picrotoxin. After muscular twitching was once obtained, the therapy revolved about maintenance of constant irritability and twitching just below the convulsive threshold. In spite of

2. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students, New York, The Macmillan Company, 1941.

all precautionary measures, however, many of the patients had short convulsions; there were apparently no untoward effects from these episodes.

Recent literature advocated the use of amphetamine as an antidote for barbiturate overdosage. Freireich and Landsberg,[3] reporting on this subject, stated they used the drug in a series of cases, their largest total dose being 400 mg. In several of the cases reported in the present paper, amphetamine was used with the picrotoxin. The chief rationale for the use of amphetamine was that it stimulated the depressed cerebral cortex, thereby supplementing picrotoxin, which acts mainly on the lower brain centers.

A third analeptic agent, "metrazol," has also been employed as a stimulant of the central nervous system.[4] The rapid response to this drug may be uitilized as an aid in the determination of the depth of coma. At periodic intervals while patients were receiving active picrotoxin therapy, we gave 1 cc. (100 mg.) of "metrazol" intravenously and observed the response. If no reaction was elicited, the dose was progressively increased to 3 cc. and the response was graded accordingly; thus, a crude estimate of the degree ot depression of the central nervous system could be made. This method was reported by Alexander,[5] who used 4 cc. of "metrazol" and classified the patients into four grades according to their response.

The presence of peripheral vascular collapse was a common complication in the severer intoxications. It may be seen from the table that 5 patients showed a dramatic fall in blood pressure. The therapeutic agents employed, besides analeptic stimulants, included plasma, isotonic solution of sodium chloride and whole blood, the amount depending on the patient's condition. A recent addition to these chemotherapeutic agents was desoxyephedrine hydrochloride, which was used both for its stimulating action on the central nervous system and for its effect of raising blood pressure.

REPORT OF CASES

CASE 5.—A 24 year old white woman ingested 100 grains (6.48 Gm.) of phenobarbital and was not hospitalized until after eighteen hours of unconsciousness. On her admission, physical examination showed her blood pressure to be

3. Freireich, A. W., and Landsberg, J. W.: Amphetamine (Benzedrine) Sulfate for Acute Barbiturate Poisoning, J. A. M. A. **131**:661-663 (June 22) 1946.

4. Androp, S.: The Use of Metrazol in Barbiturate Poisoning, Psychiatric Quart. **18**:13-22 (Jan.) 1944.

5. Alexander, F. A. D.: Amphetamine Sulfate for Acute Barbiturate Poisoning, Correspondence, J. A. M. A. **131**:1170 (Aug. 3) 1946.

The following physicians allowed us to use their clinical material: M. D. Allweiss, H. Arkin, L. Bloch, P. Daly, M. Gittleson, R. Grinker, M. Lev., E. Levine, J. Mehlman, L. Ohringer, S. Platt, R. Sternheimer and J. Reich. R. K. Richards, of Abbott Research Laboratories, North Chicago, Ill., advised us in the management of certain cases.

Data on 11 Cases of Barbiturate Poisoning

Case No.	Age	Sex	Drug and Amount Ingested	Condition on Admission	Lowest Blood Pressure	No. Hours Unconscious	Penicillin	Streptomycin	Analeptic Agents, Total Doses	Complications	Comment
1	56	M	Barbiturate and seconal sodium, amount unknown	Deep coma; absent reflexes	135–80	16			Picrotoxin, 198 mg.; desoxyephedrine hydrochloride, 40 mg.; amphetamine 40 mg.	.....	Mildly diabetic; responded well to therapy
2	22	F	Phenobarbital, amount unknown; seconal sodium 32 gr. (2.07 Gm.)?	Unconscious; only corneal and knee reflexes present	120–80	About 40	..	..	Picrotoxin, 373 mg.; desoxyephedrine hydrochloride, 60 mg; caffeine and sodium benzoate, 1.5 gr. (0.09 Gm.)	Venous occlusion of brachial vein; patient slept on arm 12 to 15 hr. before admission	Unconscious 32 hr. before hospitalization
3	43	F	Tuinal, 15 gr. (0.97 Gm.)	Unconscious; facial grimaces with orbital pressure	140–70	About 18	..	..	Picrotoxin, 250 mg., desoxyephedrine hydrochloride, 10 mg.	.....	Few mild convulsions from picrotoxin
4	23	F	Phenobarbital, 45 gr. (2.91 Gm.)?	Deep coma; absent reflexes	110–60	64	..	..	Picrotoxin, 720 mg., amphetamine, 320 mg.	Bronchopneumonia	Responded rapidly to picrotoxin (low convulsive threshold)
5	24	F	Phenobarbital, 100 gr. (6.48 Gm.)	Deep coma; absent reflexes	0–0	216	..	..	Picrotoxin, 5,139 mg.; desoxyephedrine hydrochloride, 680 mg.; metrazol, 143 cc.; caffeine and sodium benzoate, 25 Gm.	Shock 4th day of coma; bronchopneumonia; empyema in left lung	See discussion
6	48	F	Phenobarbital, 7 Gm.	Shock; required artificial respiration; absent reflex; deep coma	0–0	90	..	..	Picrotoxin, 1,017 mg.; amphetamine, 450 mg.; caffeine, 9 Gm.	Died	Radical mastectomy for carcinoma of breast 1 yr. before; multiple pulmonary and vertebral metastases noted at autopsy; bronchopneumonia
7	32	F	Seconal sodium, 90 gr. (5.82 Gm.)	Cyanosis; deep coma; absent reflex; required artificial respiration	70–90	About 78	..	..	Picrotoxin, 926 mg., caffeine, 2 Gm.	Bronchopneumonia, fever (105 F.)	Developed foot drop; urine negative for heavy metal
8	67	F	Phenobarbital(?)	Comatose; gag reflex present	118–90	48	..	..	Picrotoxin, 558 mg.	.....	Responded rapidly to picrotoxin (low convulsive threshold)
9	60	F	Seconal sodium, phenobarbital (?)	Comatose; all reflexes present	120–70	Unconscious 24 hr. prior to her admission	..	+	Picrotoxin, 225 mg., desoxyephedrine hydrochloride, 120 mg.	Abscess developed on sacrum	.....
10	32	F	Alurate sodium (?)	Deep coma; corneal reflex present	80–?	35	..	..	Picrotoxin, 760 mg., desoxyephedrine hydrochloride, 100 mg.	Numerous convulsions	.....
11	30	F	Phenobarbital, 150 gr. (9.72 Gm.)	Deep coma	60–30	135	..	..	Picrotoxin, 14,196 mg.; desoxyephedrine hydrochloride, 140 mg.; amphetamine, 1,950 mg.	Numerous convulsions; bronchopneumonia	See discussion

Note: Only patients 5 and 11 had both penicillin and streptomycin; all others just had penicillin.

120 systolic and 80 diastolic; all reflexes were absent, and there was no response to painful stimuli. Supportive therapy as outlined previously was instituted, and analeptic treatment was started at once. The patient was given picrotoxin every fifteen minutes intravenously, the highest individual dose being 15 mg. (5 cc.). During the nine days of unconsciousness, multiple complications occurred. On the fourth day in the hospital the blood pressure dropped suddenly and was unobtainable, but it was effectively restored to normal within two hours with the use of plasma and desoxyephedrine hydrochloride. A severe pneumonic infection occurred, with a localized area of dulness in the base of the left lung posteriorly. On a roentgenogram a bilateral process with a left pleural effusion was noticed, which on aspiration proved to be an encapsulated empyema. Thoracentesis and instillations of penicillin into the thoracic cavity caused remission of the ten day febrile course in forty-eight hours. This patient received both penicillin and streptomycin during the entire febrile period. Although she had numerous convulsions during the period of intensive therapy, no apparent residual effects were noted in several weeks of subsequent hospitalization. The patient received a total of 5,139 mg. of picrotoxin, a higher dose than any reported in the literature surveyed. In addition, she received 143 cc. of "metrazol," 689 mg. of desoxyephedrine hydrochloride and 25 Gm. of caffeine and sodium benzoate U.S.P.

CASE 11.—This patient, a 30 year old white woman, was hospitalized about five hours after having taken approximately 150 grains (9.72 Gm.) of phenobarbital. The initial response to 15 mg. of picrotoxin given intravenously was good, that is, twitching resulted. Within eight to ten hours, however, extreme deterioration occurred. Whereas corneal and gag reflexes were present on her admission, these could no longer be elicited, and respiratory depression had become pronounced. A test dose of 1 cc. "metrazol" administered intravenously along with the picrotoxin on her admission had evoked a brief convulsion; but now the patient was no longer stimulated by 3 cc. of "metrazol," which signified roughly the increasing depth of coma. Since the patient no longer responded to the orthodox therapy recommended, we felt that more radical doses must be administered. The usual 15 mg. dose was progressively increased to 45 mg. (15 cc.) every fifteen minutes. At this level we were once again able to obtain a preconvulsive state. Clinically, the patient showed early signs of improvement with the elevated dose; the blood pressure rose, and the respiratory exchange was improved. In the course of several hours this dose was reduced slowly to lower levels, with constant maintenance of an irritable state. The patient received more than 15 mg. of picrotoxin every fifteen minutes for more than one hundred and four hours. At the end of the fifth day of unconsciousness, the patient opened her eyes and responded to simple instructions. An attempt was made to stop all therapy, but within one hour the patient slipped back into coma, and vigorous therapy was again resumed. By the end of the next twenty-four hours the patient was talking and sipping fluids, but constant stimulation was required to maintain this state for another twelve hours. The fact that barbiturates were present in the urine on the eighth day after her return to consciousness explained the necessity for constant stimulation to prevent relapse. This case, like many others, was complicated by extensive bronchopneumonia. Penicillin and streptomycin were given from the beginning of therapy, in spite of which the patient's illness ran a stormy, febrile course. Aerosol penicillin was instituted once the patient was conscious to help stem the severe bronchopneumonia. During the period of unconsciousness, an acute gastric dilatation occurred, requiring Wangensteen suction for several days. The patient received 14,196 mg. of picrotoxin, and 1,950 mg. of amphetamine

were given concomitantly in doses of 10 to 30 mg. intravenously. To our knowledge, the total dose of picrotoxin is the highest recorded in current literature. At the end of two weeks the patient was no longer considered a medical problem and was transferred to the department of psychiatry.

COMMENTS AND CONCLUSIONS

Severe barbiturate poisoning may require much larger doses of picrotoxin than those usually recommended. It is our experience that no arbitrary dose exists in this regard. The amount of picrotoxin given must be varied according to the depth of coma, which can be judged not only by the amount of intoxicant ingested and the time elapsed before treatment is instituted, but also by the patient's response to the previous dose of picrotoxin. While a patient is comatose, there is no toxic dose of picrotoxin until a preconvulsive state is reached. The average dose administered during the acute phase was 15 mg. every fifteen minutes.

"Metrazol" is a valuable aid in the estimation of the depth of coma.

It should be emphasized that after the patient begins to respond to smaller and smaller doses of picrotoxin with preconvulsive twitchings, indicating an awakening of the lower brain centers, therapeutic stimulation of the cortex by amphetamine is indicated, since picrotoxin is not primarily a cortical stimulant. If all medication is stopped as soon as the patient begins to awaken, he will go back into coma, especially when barbital or phenobarbital has been ingested, since these drugs are excreted slowly. In 1 of our cases, phenobarbital was still being excreted in the urine five days after consciousness first returned.

Maintenance of fluid balance, constant vigilance in keeping the air passages clear and, above all, immediate administration of antibiotic substances to help prevent pulmonary infection are necessary if the analeptic agents are to have a chance to reverse the intoxication. If these measures are not instituted, the patient may die before sufficient time has elapsed to allow neutralization of the intoxicants.

All 11 patients in this series received penicillin; bronchopneumonia developed in 4 of the patients while they received penicillin therapy. The 2 patients reported on in detail (cases 5 and 11) were given both streptomycin and penicillin; 1 patient (case 5) had a complicating encapsulated empyema which responded to local instillations of penicillin into the thoracic cavity. The other patient (case 11) recovered from bronchopneumonia only when aerosol penicillin was added to the usual parenteral administration of antibiotic drugs.

It is apparent that medical therapy is only the beginning of treatment, which should in all cases be continued by placing the patient in the hands of a psychiatrist.

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Progress In Internal Medicine

ALLERGY

A Review of the Literature of 1946 and 1947

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IN THE two years that have elapsed since the review of the literature of 1944 and 1945 was presented[1] several advances in knowledge have been made.

The first is a dramatic advance. It concerns the antihistaminic drugs which late in 1945 were hailed as a possible panacea for allergic diseases of every kind. A large number of papers have described the many aspects of it. The second is more clinical and practical; it concerns the psychosomatic factors which are being recognized more and more in the cause of asthma. The third is the new development in the understanding of the pathologic aspects of asthma and kindred states and their relation to similar lesions produced by a similar mechanism in other diseases. Finally, the treatment of patients has been improved by the method of administering drugs directly to the nasal and bronchial mucosa in the form of a fine spray, or "aerosol."

It is to be noted that these forward steps have been taken not by the workers in allergy itself but by investigators in other fields. It is their work in pharmacology and pathology which finds application in allergy. Through their work, the concept of the causes of asthma has been widened materially, and through it the concept of allergic reactions as important factors in other diseases besides asthma, hay fever, urticaria and eczema has been advanced. The phrase "all is not allergy that wheezes" has found ample support.

In the last review I pointed out that the production of symptoms in allergic diseases required four distinct steps. First, the asthmatic state, the "X" factor, is essential, for it explains why hay fever, asthma or eczema develop in only certain persons. In persons with a "Y" factor arthritis might develop, or in a third group, with a "Z" factor, mucous colitis might develop, or perhaps migraine headaches or peptic ulcer.

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1. Rackemann, F. M.: Allergy: A Review of the Literature of 1944 and 1945, with Comments on Future Problems, Arch. Int. Med. **77**:700 (June) 1946; **78**:108 (July) 1946.

In each case the patient is "conditioned," so that when exciting causes and other factors come to him chronic disease of a certain type peculiar to his predisposition develop. It is interesting to observe that it is uncommon for more than one of these chronic disease groups to develop in a patient. The patients with asthma almost never have peptic ulcer.

Granted the asthmatic state in the background, the theory is that the second step has one of four different mechanisms, any one of which can release a histamine-like substance to constitute the third step, and this in turn can produce any one of a variety of symptoms as the fourth step. The typical mechanism of the second step is the antigen-antibody reaction of allergy, but there is reason to think that infectious processes can cause the same release of H substance. Intoxication by drugs, like the sulfonamide drugs, can do the same thing, and then, of greater interest, is the concept that depletion (a general lowering of the vitality, whether on a somatic or psychic basis) can also release H substance and produce the symptoms which together constitute clinical allergy.

The current literature, in the order of these four steps, may be considered in two parts: Part I includes the first three steps through the release of histamine. It is a complex process which involves the review of experimental evidence. Part II is more clinical: the review of recent advances in pathology, in diagnosis and in treatment.

PART I. MECHANISM OF SYMPTOM PRODUCTION

THE ASTHMATIC STATE

Ever since 1932, when Weiss, Robb and Ellis[2] first observed that the patient with asthma reacted to an intravenously administered dose of histamine differently than did the normal person, it has been recognized that the difference is basic. New papers confirm the observation. Curry[3] took repeated measurements of the vital capacity while injecting histamine intravenously in small amounts into patients with asthma and normal persons. Only in the former group did the figure fall. Later, Curry[4] compared the effect of methacholine chloride ("mecholyl chloride") (acetyl-beta-methylcholine) with histamine and observed it to be even more active in reducing the vital capacity. In normal persons neither

2. Weiss, S.; Robb, G. P., and Ellis, L. B.: The Systemic Effects of Histamine in Man, with Special Reference to the Responses of the Cardiovascular System, Arch. Int. Med. **49**:360 (March) 1932.

3. Curry, J. J.: The Action of Histamine on the Respiratory Tract in Normal and Asthmatic Subjects, J. Clin. Investigation **25**:785, 1946.

4. Curry, J. J.: Comparative Action of Acetyl-Beta-Methyl Choline and Histamine on the Respiratory Tract in Normal Patients with Hay Fever and Subjects with Bronchial Asthma, J. Clin. Investigation **26**:430, 1947.

histamine nor "mecholyl chloride" produced any change in the vital capacity. Rose[5] also has worked with injections of histamine, observing that whereas peripheral vasodilatation (flushing) occurs in all subjects, whether allergic or not, asthma, urticaria or headache occurred only in those who were predisposed to these allergic manifestations.

The factor of one's constitution is as important as it is obscure. Resistance to the common cold, for example, has been shown by Sargent, Lombard and Sargent[6] to be rather stable. In a large boarding school each boy had the same number of colds, some more and some less than the average, but each year the same. Constitution is inherited, and now Stiles and Johnston[7] present another study of inheritance. In a family of 232 persons, asthma and hay fever occurred in 22.4 per cent, in contrast to the figure of about 7 per cent for the general population. The concept of a constitutional abnormality—of an "asthmatic state"—in certain susceptible persons is justified.

The Theory of the Release of Histamine.—That antigen-antibody reactions can release H substance is the heart and soul of allergy. The fact goes far to explain the precipitation of a typical group of symptoms by reactions set up by a wide variety of specific foreign substances. That much is clear. Can the same symptoms, dependent on the release of the same H substance, be precipitated by other mechanisms—infection, intoxication and especially depletion? It is the observation in patients in the clinic which indicates that these other factors must be important.

In a recent paper[8] I described a working classification of asthma. The patients in whom asthma begins before the age of 30 are usually allergic, and their asthma should be considered as dependent on allergy until proved otherwise. The methods of allergy appear to be adequate in diagnosis and treatment. A study of the older age group is more interesting; when asthma begins after the age of 40, it is my opinion that the cause should be considered as something other than allergy until proved otherwise. When in a young person asthma becomes severe, so that the patient must be admitted to the hospital, great improvement frequently follows within three days, the patient probably having escaped from a dust which was causing trouble at home. In an older

5. Rose, B.: Role of Histamine in Anaphylaxis and Allergy, Am. J. Med. **3**:545, 1947.

6. Sargent, F.; Lombard, O. M., and Sargent, V. W.: Further Studies on Stability of Resistance to the Common Cold, Am. J. Hyg. **45**:29, 1947.

7. Stiles, K. A., and Johnston, E. J.: Study of Inheritance of Respiratory Allergies, J. Allergy **17**:11, 1946.

8. Rackemann, F. M.: Working Classification of Asthma, Am. J. Med. **3**:601, 1947.

person, however, the asthma continues even in the new and clean environment, the cause being something which the patient carries with him. The asthma is "intrinsic."

There are various theories to explain this "intrinsic" asthma. In his new book Cooke[9] describes "infective" asthma. He expresses the belief that new colds are a satisfactory explanation for the kind of asthma which occurs in children and young adults at long intervals and in short seizures; he agrees with me that for this group the term "asthmatic bronchitis" is satisfactory. Whether the more persistent asthma which begins rather suddenly in men and women past the age of 40 can be attributed to a form of allergy to the bacteria involved in the focus of infection, or perhaps in the diffuse infection of the sinuses and bronchi, is obviously the important question. The diffculty about demonstrating this allergy through cutaneous tests has made it difficult to explain the process of this basis with real finality.

In a more recent paper Cooke[10] places his "infective" asthma under the general heading of delayed inflammatory reactions, implying that reactions to cutaneous tests of the immediate urticarial wheal and erythema variety need not be expected in this group. When cutaneous tests with intradermal injections of whole organism vaccines or filtrates of broth cultures are made inflammatory reactions are often observed in twenty-four hours. Rarely does one see an immediate wheal and erythema reaction after administration of vaccines. Cutaneous tests with the carbohydrate fractions should be made, for, as Francis and Abernathy[11] showed long ago, it is the soluble specific substance contained in the carbohydrate which gives the immediate reaction. There are difficulties with both types of tests. Delayed inflammatory reactions of the tuberculin type point, like tuberculin itself, to the past history of the patient as much as to his present illness. One needs only to consider the fallacy that the demonstration of a positive reaction to tuberculin could prove that the asthma is tuberculous in origin.

Tests with bacterial carbohydrates may become more interesting, but the high degree of specificity among bacterial species imposes considerable practical difficulties. The test requires carefully made cultures, and it requires a rather complex technic for isolating the carbohydrate fraction from the various bacteria isolated. The problem is not easy, but it should be investigated.

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9. Cooke, R. A., and others: Infective Asthma with Pharmacopeia, in Cooke, R. A.: Allergy in Theory and Practice, Philadelphia, W. B. Saunders Company, 1947, chap. 7, p. 130.

10. Cooke, R. A.: Immunology of Allergic Disease, Am. J. Med. **3**:523, 1947.

11. Francis, T., Jr., and Abernathy, J. J.: Cutaneous Reactions in Pneumonia to a Somatic "C" Polysaccharids of Pneumococcus, read before the Society for Clinical Investigation, May 1934.

Intoxication due to drugs, as a mechanism for the release of H substance, will be discussed under allergy due to drugs. No direct observations have been made, and the concept depends almost entirely on clinical evidence. This, however, demonstrates that drugs can cause allergic symptoms as well as can pollens, animal danders or even foods.

Depletion has been described by me[12] as a cause of asthma. The conception of Selye,[13] with his discussion of the general adaptation syndrome, was noted in a previous review. His thesis is that stress and strain, whether of physical, infectious or emotional origin, can give rise to a number of changes in the body and that asthma may be one of these. This concept is in agreement with my own idea[12] that depletion may be in itself an adequate cause of asthma. In patients who are conditioned, as it were, by having the asthmatic state, depletion, or, perhaps better, stress and strain of various kinds, can produce the same symptoms which follow the ordinary antigen-antibody reaction of allergy. (The conditioning is important.) Since in many cases the depletion comes first and the asthma follows, one has to think of a cause and effect relationship. The clinical picture includes loss of weight, strength and courage, but it also includes rather typical exhaustion, which has been termed "allergic toxemia." One observes a low temperature, low blood pressure, rapid pulse rate and low white cell count. Clinical observation indicates that the factor of depletion is real.

Depletion may be somatic and may develop because of malnutrition or perhaps because of some more definite disturbance, like abscessed teeth or a focal infection in the sinuses, gallbladder or elsewhere, but depletion can also be of psychic origin, and there is increasing clinical evidence to support that theory. Henderson[14] writes about the psychogenic factors in bronchial asthma. Brown and Goitein[15] and Metzger[16] lay stress on the emotional aspects of their patients with asthma, and Gliebe and Kerr[17] present a number of interesting histories of patients, each of whom was relieved simply by appropriate reeducation. Miller, and

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12. Rackemann, F. M.: Depletion in Asthma, Tr. Am. Clin. & Climatol. A. **58**:71, 1946.

13. Selye, H.: The General Adaptation Syndrome and the Disease of Adaptation, J. Allergy **17**:231, 289 and 358, 1946.

14. Henderson, A. T.: Psychogenic Factors in Bronchial Asthma, Canad. M. A. J. **106**:55, 1946.

15. Brown, E. A., and Goitein, P. L.: The Meaning of Asthma, Psychoanalyt. Rev. **31**:299, 1944.

16. Metzger, F. C.: Emotions in the Allergic Individual, Am. J. Psychol. **103**:697, 1947.

17. Gliebe, P. A., and Kerr, W. J.: Recognition of Emotional Factors in Allergic Manifestations, Am. J. Med. **3**:607, 1947.

Baruch[18] told stories of children who were frustrated in various ways and learned to use their asthma as an escape mechanism. In discussion of this paper, Dr. J. H. Mitchell pointed out that in the young group male and female patients are about equal in number, but in the older group women outnumber the men 2 to 1. In other papers one reads of actual cases or of the suggestion that nervous factors were predominant in the particular problem. I am learning to pay close attention to the emotional aspects as well as to the physical environment of the patient.

What objective evidence is there to support this concept of depletion? Wolff[19] studied the mucous membrane of the stomach in a patient who came to him with gastric stoma, like that of Alexis St. Martin, the patient of William Beaumont. When this boy was frightened decided vasoconstriction, both of the gastric membrane and of the nose, became apparent, and then when fear turned to rage the opposite took place—redness and swelling developed at once. Fowler[20] described a soldier whose nose became pale and boggy as long as he was in the army, but on discharge all his symptoms cleared away.

Frabricant[21] describes the rapid shift in the p_H of the nasal secretions, from slightly acid to alkaline, which fright could induce in 3 of his patients.

Brown and Venning[22] show that emotional disturbances, as well as burns, infections, fractures and operations, can result in a rapid increase in the urinary excretion of the glocogenic corticoid hormones, thus indicating an increase of the activity of the adrenal cortex. Forbes and her co-workers[22a] have observed that under conditions of stress the 17-ketosteroids are increased at first and fall to subnormal values later. Brown[23] submits the report of a man aged 34, with many allergic symptoms, who was relieved by taking diphenhydramine hydrochloride ("benadryl hydrochloride") 50 mg. twice a day. With the medication

18. Miller, H., and Baruch, D. W.: Group and Individual Psychotherapy as an Adjunct in the Diagnosis and Treatment of Allergy, read before the American Academy of Allergy, New York, Nov. 25, 1946, unpublished data.

19. Wolff, H. A.: Life Situations, Emotions and Nasal Functions: A Report on Research, read before the American Society for Research in Psychosomatic Problems, New York, Feb. 15, 1946.

20. Fowler, E. P., Jr.: A Nose and Throat Viewpoint, read before the American Society for Research in Psychosomatic Problems, New York, Feb. 15, 1946.

21. Fabricant, N. D.: Effect of Emotions on the Hydrogen Ion Concentration of Nasal Secretion in Situ, with Comment on Terminology of Nasal Hydrogen Ion Concentration Measurement, Arch. Otolaryng. **43**:402 (April) 1946.

22. Browne, J. S. L., and Venning, L. H.: The Response of the Adrenal Cortex to Disease and Trauma, Tr. A. Am. Physicians **60**:16, 1947.

22a. Forbes, A. P.; Donaldson, E. C.; Reifenstein, E., Jr., and Albright, F.: The Effect of Trauma and Disease on the Urinary 17-Ketosteroid Excretion in Man, J. Clin. Endocrinol. **7**:264 (April) 1947.

23. Brown, W. T.: The Probable Role of Histamine in Some Emotionally Precipitated Allergic Conditions, Yale J. Biol. & Med. **19**:63, 1946.

his emotions did not cause asthma any more. It is obvious that the authors of these papers agree with Dr. Cannon,[24] who originally demonstrated that emotion can produce physiologic changes.

An argument against the idea that depletion is concerned with antigen-antibody reactions of any kind occurs in a paper by Vezina.[25] He talks about "fasting immunity," or "malnutrition immunity," pointing out that neither prisoners of war nor poorly nourished infants are particularly subject to infection. He cites Sprunt[26] as well as Foster and his co-workers,[27] who observed that vaccines and viruses do not survive well in animals whose cells have been deprived of certain important nutriments. This paper encourages the suggestion that depletion, which clinically is a satisfactory explanation in certain cases, depends more on a physiologic disturbance of hormones, or other factors, than on any influence on immune processes, whether concerned with allergy to dusts or foods or with the reactions to infections.

None of this previous work deals with the actual release of H substance by infection or by stress and strain. So far one can only assume that since depletion, as well as infection, intoxication and allergy itself, can cause asthma and kindred allergic symptoms, the mechanism is by way of the release of H substance. Further study of histamine itself and, especially, of the new antihistaminic drugs will help to clarify the problems. As said in the opening paragraph, it is the discovery and distribution of the antihistaminic drugs which constitute the dramatic advance since 1945.

Histamine Release.—A number of good reviews have been written on the subject of histamine and the antihistaminic drugs. In 1943, Dragstedt[28] wrote "The Significance of Histamine in Anaphylaxis and Allergy." Rocha e Silva[29] in 1944 published "Recent Advances in the Histamine Problem." He emphasized the observation that other mechanisms besides the antigen-antibody reaction could release hista-

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24. Cannon, W. B.: The Wisdom of the Body, New York, W. W. Norton & Company, Inc., 1932.

25. Vezina, N.: L'immunité par la sous-alimentation, Union méd. du Canada **76**:971, 1947.

26. Sprunt, D. H.: Effect of Undernourishment on Susceptibility of Rabbit to Infection with Vaccinia, J. Exper. Med. **75**:297, 1942.

27. Foster, C.; Jones, J. H.; Henle, W., and Dorfman, F.: The Comparative Effects of Vitamin B_1 Deficiency and Restriction of Food Intake on the Response of Mice to the Lansing Strain of Poliomyelitis Virus, as Determined by the Paired Feeding Technique, J. Exper. Med. **80**:257, 1944.

28. Dragstedt, C. A.: The Significance of Histamine in Anaphylaxis and Allergy, Quart. Bull., Northwestern Univ. M. School **17**:102, 1943; The Significance of Histamine in Anaphylaxis, J. Allergy **16**:69, 1945.

29. Rocha e Silva, M.: Recent Advances Concerning the Histamine Problem, J. Allergy **15**:399, 1944; Histamine with Anaphylaxis, Sao Paulo, Brazil, Grafica e Editores Edigraf Ltd., 1946.

mine. He demonstrated that animal poisons, like snake venom and bee venom, can release histamine by an action which runs rather parallel to the hemolytic activity of these substances. Trypsin also releases histamine from cells, especially in the liver, and treatment with trypsin results in an increase of histamine in the blood plasma. Arginine and histidine, on the other hand, counteract the histamine effect. These amino acids contain an imino- group (NH) which anchors the histamine to the tissues by a peptid linkage. Histamine which is bound to the cell is rather inactive. In the test tube the peptid linkage is easily broken down by acid hydrolysis; in the body it may be broken by proteolytic enzyme, the so-called intracellular cathepsin of the tissue fluids. The reason that bee venom is so poisonous is that it, too, can break the linkage and allow bound histamine to become free plasma histamine. Peptone and specific antigens release histamine by a similar chemical mechanism. One should note that the clinical symptoms of all these processes, whether from an antigen-antibody reaction, bee sting or injection of peptone or trypsin, are the same. As Dragstedt says, the histamine theory is at least plausible.

More recently, Rose[5] of Montreal has presented a useful and comprehensive discussion of this problem. He lays stress on the ready shift between bound histamine and free histamine.

The experiment of Katz[30] is important. In 1940 Katz showed that when horse serum was added in vitro to the blood of a rabbit sensitized with horse serum the amount of histamine in the cell-free plasma increased greatly. Rose and Browne[31] confirmed this experiment. When egg albumin was added to the blood of an egg-sensitive rabbit, the amount of histamine in the plasma increased to ten times the amount obtained when the same blood was mixed with isotonic solution of sodium chloride and five times the amount when it was mixed with horse serum. It is the interchange which explains the irregularity in the measurements of histamine in the circulating blood. The method of assay requires heating of the specimen in the presence of acid, and this treatment is enough to break the linkage and convert all the histamine present into free unbound histamine. The method, therefore, indicates the total histamine and not merely the free histamine in the sample. Rocha e Silva[29] bound histamine to amino acids artificially and then observed that, whereas the combination had no physiologic action,

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30. Katz, G.: The Role of Blood Cells in the Anaphylactic Histamine Release, J. Pharmacol. & Exper. Therap. **72**:22, 1941. Katz, G., and Cohen, S.: Experimental Evidence for Histamine Release in Allergy, J. A. M. A. **117**:1782 (Nov. 22) 1941.

31. Rose, B., and Browne, J. S. L.: Studies on the Release of Histamine from the Blood Cells of the Rabbit by the Addition of Horse Serum or Egg Albumin in Vitro, J. Immunol. **41**:403, 1941.

31a. Rose, B.: Personal communication to the author.

the assay for histamine which destroyed the linkage in the process showed the original amount still present. If this shift can occur from blood to tissue cells as well as from plasma to blood cells and back again, it is not surprising that the amount of histamine seen in a given specimen of blood does not run parallel to the severity of allergic symptoms. One gets the impression that histamine can change from the free to the bound state and back again rather readily. Rose points out, however, that, whereas the evidence of transfer from the bound to the free state is ample, there is not yet any direct method for showing the reverse, namely, a shift from the free to the bound state. In his review, Rose[5] recalls that Code[32] showed that in anaphylaxis in dogs there is in the early stages a rapid release of free histamine, but as the process continues death may occur at a time when the amount of histamine in the blood has become normal again. The last two sentences of Rose's paper[5] are quoted:

> It seems probable that small amounts of histamine may be continually released in some cases of allergy producing local symptoms, and rapidly removed by means of kidney or intestine as evidenced by the increased histamine content of urine and feces under these conditions. A marked increase in the total blood histamine without alteration of the plasma histamine is completely compatible with absence of symptoms.

This change in the state of histamine from being bound to cells to being free in the plasma makes it difficult to analyze the process in allergy. So far the literature contains few references to the comparative measurements of free histamine in the plasma with bound histamine in the blood cells in patients. It appears to me that further study of this aspect might be fruitful. Meantime, other mechanisms are undoubtedly involved, and it is the antihistaminic drugs and the study of their pharmacologic aspects which have provided the best evidence that the complete explanation does not lie in histamine itself. In the next section are brought out the several discrepancies between the effects of these drugs in experiments with histamine and their effects in experiments involving antigen-antibody reactions.

Antihistaminic Drugs.—There are three ways in which the effect of histamine can be inhibited. First, it has been said that histamine could be destroyed by a ferment histaminase. In experiments with animals the ferment was often effective, but in human beings the results of treatment with histaminase have been disappointing. Second, attempts to increase the natural resistance against histamine have been made, sometimes by repeated injections of histamine itself, sometimes by using the histamine azoprotein called "hapamine" (a chemical combination of histamine and despeciated horse serum globulin), which Fell,

32. Code, C. F.: The Histamine Content of the Blood of Guinea Pigs and Dogs During Anaphylactic Shock, Am. J. Physiol. **127**:78, 1939.

Rodney and Marshall[33] first produced in 1943. In both cases, however, the results have been disappointing. Neither with histamine nor with "hapamine" has the treatment been effective. The third method is more recent, and results are much more dramatic. A series of new compounds, referred to as antihistaminic drugs, has been developed. They can neutralize histamine in the test tube. These drugs include certain aromatic derivatives of aminoethanol and ethylenediamine, as well as benzohydryl ethers of beta-dimethylaminoethanol. All are closely related, and all are able to antagonize histamine without eliciting pharmacologic responses. They do not, like epinephrine, produce an opposing effect. The literature on these drugs has been reviewed in two papers by Feinberg.[34] The pharmacologic aspects of antihistamine compounds have been reviewed in detail by Loew.[35] The important points are as follows:

In 1933 Fourneau and Bovet[36] developed their compound "929 F" (thyroxyethyldiethylamine), and in 1937 Staub and Bovet[37] described its antihistaminic properties. It protected guinea pigs against two lethal doses of histamine. Twelve years later the new drug tripelennamine hydrochloride ("pyribenzamine hydrochloride") was observed to be from one thousand to ten thousand times as active against histamine as was "929 F." "Benadryl" and "pyribenzamine" are the two drugs which are available for clinical use today. "Antergan" (dimethylamino-ethyl benzylaniline) and "neoantergan" (N-p-methoxybenzyl-N-dimethyl-aminoethyl *a* aminopyridine) are less well known. New and even better preparations are being manufactured. "Benadryl" (beta-dimethylamino-ethyl benzohydryl ether hydrochloride) was developed by Loew and his associates[38] in the laboratories of Parke, Davis & Company in February 1945. "Pyribenzamine" (N pyridyl-N benzyl-N-dimethylethylenedia-

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33. Fell, N.; Rodney, G., and Marshall, D. E.: Histamine-Protein Complexes: Synthesis and Immunologic Investigation; Histamine-Azoprotein, J. Immunol. **47:237, 1943.**

34. Feinberg, S. M.: Histamine and Antihistaminic Agents: Their Experimental and Therapeutic Status, J. A. M. A. **132:702** (Nov. 23) 1946; The Antihistaminic Drugs: Pharmacology and Therapeutic Effects, Am. J. Med. **3:560, 1947.**

35. Loew, E. R.: Pharmacology of Antihistaminic Compounds, Physiol. Rev. **27:542, 1947.**

36. Fourneau, E., and Bovet, D.: Recherches sur l'action sympathicolytique d'un nouveau dérivé du dioxane, Arch. internat. de pharmacodyn. et de thérap. **46:178, 1933.**

37. Staub, A. M., and Bovet, D.: Action de la thymoxyéthyldiéthylamine (929 F.) et des ethers phénoliques sur le choc anaphylactique du cobaye, Compt. rend. Soc. de biol. **125:818, 1937.**

38. Loew, E.; Kaiser, M. E., and Moore, V.: Synthetic Benzhydryl Alkamine Ethers Effective in Preventing Fatal Experimental Asthma in Guinea Pigs Exposed to Atomized Histamine, J. Pharmacol. & Exper. Therap. **83:120, 1945.**

mine) was developed by Mayer, Huttrer and Scholz[39] in the laboratories of the Ciba Pharmaceutical Products, Inc., in July 1945.

"Antergan" (N phenyl-N benzyl-N-dimethylethylenediamine) was developed by Halpern[40] from compounds synthesized by Mosnier in the laboratories of the Rhone-Poulenc Society in France in 1942.

"Neoantergan" (N-p-methoxybenzyl-N-dimethylaminoethyl a aminopyridine) appeared two years later, being made by Bovet and associates[41] in France. (One observes that the French did this important work despite the war and, also, that the French, in their laboratories, were about three years ahead of us.) These four formulas are much alike, and their pharmacologic actions are rather similar.

The clinical results of the use of "benadryl" and "pyribenzamine" as reported in the literature are so numerous that it is best to review them as a series of tables. To make the figures as comparable as possible, I have added the figures for "excellent" results to the figures for "good" results.

TABLE 1.—*Results of Treatment for Hay Fever*

Author	No. Cases	Results		
		Excellent and Good		Poor
		No. of Cases	Percentage	No. of Cases
		TREATMENT WITH "BENADRYL"		
Friedlaender (Footnote 53)	19			19
Logan (Footnote 44)	12	9	75	3
Mc Elin and Horton (Footnote45)	22	21	94	1
Koelsche, G. A.; Prickman, L. E., and Carryer, H. M. J. Allergy 17:151, 1946; Proc. Staff Meet., Mayo Clin. 20:432, 1945	52	39	75	13
Waldbott (Footnote 48)	31	23	74	8
Levin (Footnote 52)	78	46	59	32
McGavack, Elias and Boyd (Footnote 47)	8	6	75	2
Eyermann, C. H.: J. Allergy 17:210, 1946	52	47	90	5
Friedlaender and Feinberg (Footnote 54)	19	2	10	17
Wagner (Footnote 49)	38	24	63	14
Loveless, M. H., and Brown, H.: New England J. Med. 237:501, 1947	38	31	81	7
Bernstein, Rose and Feinberg (Footnote 42)	54	28	52	26
Blumenthal, L. S., and Rosenberg, M. A.: J.A.M.A. 135:20 (Sept. 6) 1947	23	15	65	8
Total for "benadryl"	446	291	66	155 (34%)
		TREATMENT WITH "PYRIBENZAMINE"		
American Academy of Allergy (Footnote 50)	104	56	54	48
Arbesman, Koepf and Lenzner (Footnote 51)	140	119	85	21
Loveless, M. H., and Brown, H.: New England J. Med. 237:501, 1947	60	51	85	9
Bernstein, Rose and Feinberg (Footnote 42)	254	208	82	46
Henderson and Rose (Footnote 43)	61	47	77	14
Total for "pyribenzamine"	619	481	77	138 (22%)

39. Mayer, R. L.; Huttrer, C. P., and Scholz, C. R.: Antihistaminic and Anti-anaphylactic Activity of Some a-Pyridino-Ethylenediamines, Science **102**:93, 1945.

40. Halpern, B. N.: Etude expérimental des antihistaminiques de synthèse: Essais de chimothérapie des états allergiques, J. de méd. de Lyon **23**:409, 1942.

41. Bovet, D.; Horclois, R., and Walthert, F.: Propriétés antihistaminiques de la n-p-méthoxybenzyl-n-diméthylaminoéthyl *a* amino-pyridine, Compt. rend. Soc. de biol. **138**:99, 1944.

In hay fever (table 1) the total results with "benadryl" were good, and often excellent, in 66 per cent of the cases, but the figures vary and many of the groups were small. With "pyribenzamine" the results were better—77 per cent good results.

In chronic vasomotor rhinitis (table 2) the results of treatment with "benadryl" have been reported by Bernstein, Rose and Feinberg,[42] by

TABLE 2.—*Results of Treatment for Vasomotor Rhinitis with "Benadryl" and "Pyribenzamine"*

Author	No. of Cases	Results			
		Excellent and Good		Poor	
		No. of Cases	Percentage	No. of Cases	Percentage
		TREATMENT WITH "BENADRYL"			
Bernstein, Rose and Feinberg (Footnote 42)	40	7	17	33	82
Henderson and Rose (Footnote 43)	21	13	62	8	38
Eight Authors (referred to in text)	104	64	61	40	38
Total for "benadryl"	165	84	51	81	49
TREATMENT WITH "PYRIBENZAMINE"					
American Academy of Allergy (Footnote 50)	277	164	59	113	41
Arbesman, Koepf and Lenzner (Footnote 51)	138	100	72	38	27
Bernstein, Rose and Feinberg (Footnote 42)	130	83	64	47	36
Total for "pyribenzamine"	545	347	63	198	36

Henderson and Rose[43] and by eight other authors including Logan[44] (2 cases, McElin and Horton[45] (8 cases), Williams[46] (12 cases), McGavack, Elias and Boyd[47] (11 cases), Waldbott[48] (23 cases) and Wagner[49] (30 cases). In 165 patients treated with "benadryl," the results were excellent and good in 51 per cent. With "pyribenzamine" the members of the American Academy of Allergy[50] reported good results in 59 per cent of 277 cases. Arbesman and his associates[51] obtained good results in 100 out of 138 cases, or 72 per cent, and the figures of Bernstein and his associates[42] fall between. The total figure with "pyribenzamine" was better than with "benadryl." It is interesting that in 35 cases of what Arbesman called "intrinsic nonseasonal rhinitis" the results with "pyribenzamine" were good in only 48 per cent.

42. Bernstein, T. B.; Rose, J. M., and Feinberg, S. M.: New Antihistaminic Drugs (Benadryl, Pyribenzamine, and Neoantergan) in Hay Fever and Other Allergic Conditions, Illinois M. J. **92**:8, 1947.

43. Henderson, A. T., and Rose, B.: Pyribenzamine (N-Pyridyl, N-Benzyl, Dimethyl-Ethylenediaminehydrochloride) in the Treatment of Allergy, Canad. M. A. J. **57**:136, 1947.

44. Logan, G. B.: The Use of Benadryl in Allergic Diseases of Childhood, Proc. Staff Meet., Mayo Clin. **20**:436, 1945.

45. McElin, T. W., and Horton, B. T.: Clinical Observations on the Use of Benadryl; A New Antihistaminic Substance, Proc. Staff Meet., Mayo Clin. **20**:417, 1945.

(Footnotes continued on next page)

Table 3 shows the results in asthma. In the total number, the results with "benadryl" were excellent and good in 42 per cent. Here the combined results with "benadryl" are somewhat better than the results with "pyribenzamine," but treatment with neither drug is really good in asthma. Waldbott[48] and Wagner[49] distinguish between seasonal asthma,

TABLE 3.—*Results of Treatment for Asthma*

Author	No. of Cases	Results		
		Excellent and Good		Poor
		No. of Cases	Percentage	No. of Cases
		TREATMENT WITH "BENADRYL"		
Friedlaender (Footnote 53)	9			9
Eyermann, C. H.: J. Allergy 17:210, 1946	16	6	38	10
Friedlaender and Feinberg (Footnote 54)	16			16
Koelsche, G. A.; Prickman, L. E., and Carryer, H. M.: J. Allergy 17:151, 1946; Proc. Staff Meet., Mayo Clin. 20:432, 1945	12	4	33	8
Waldbott (Footnote 48)				
Perennial bronchial asthma	48	24	50	24
Seasonal bronchial asthma	30	14	49	16
Levin (Footnote 52)	87	57	65	30
McGavack, Elias and Boyd (Footnote 47)	36	30	83	6
Wagner (Footnote 49)				
Seasonal asthma	20	8	40	12
Intrinsic asthma	42	10	24	32
Fuchs, A. M.; Schulman, P. M., and McGavack, T. H.: North Carolina M. J. 7:141, 1946	30	7	23	23
Bernstein, Rose and Feinberg (Footnote 42)	50	6	12	44
Total for "benadryl"	396	166	42	230 (58%)
		TREATMENT WITH "PYRIBENZAMINE"		
American Academy of Allergy (Footnote 50)	222	70	31	152
Arbesman, Koepf and Lenzner (Footnote 51)				
Grasses	12	6	50	6
Extrinsic (other than pollens)	62	28	45	34
Bernstein, Rose and Feinberg (Footnote 42)	121	33	28	88
Total for "pyribenzamine"	417	137	33	280 (67%)

due presumably to pollen and therefore allergic, and perennial asthma, due to other causes. Wagner had much better results in the allergic extrinsic group. In Waldbott's two groups, however, the results were the same. In this table one observes that Levin[52] obtained good results

46. Williams, H. L.: Use of Benadryl in the Syndrome of Physical Allergy of the Head: A Preliminary Report, Proc. Staff Meet., Mayo Clin. **20**:434, 1945. (Benadryl): Its Use in Allergic Diseases, J. Allergy **17**:145, 1946.

47. McGavack, T. H.; Elias, H., and Boyd, L. J.: Some Pharmacological and Clinical Experiences with Dimethylaminoethyl Benzyhydryl Ether Hydrochloride (Benadryl), Am. J. M. Sc. **213**:418, 1947.

48. Waldbott, G. L.: Clinical Results with Benadryl, J. Allergy **17**:142, 1946.

49. Wagner, H. C.: The Use of the New Antihistaminic Substances in the Treatment of Allergic Disorders, M. Clin. North America **31**:43, 1947.

50. A Report of the Clinical Studies on the Use of Pyribenzamine in Allergic Diseases, the Committee on Pharmaceuticals and Medicaments of the American Academy of Allergy, J. Allergy **17**:325, 1946.

51. Arbesman, C. E.; Koepf, G. F., and Lenzner, A. R.: Clinical Studies with N'Pyridyl, N'Benzyl, Dimethylethylenediamine Monohydrochloride (Pyribenzamine), J. Allergy **17**:275, 1946.

in 65 per cent of 87 cases, whereas neither Friedlaender[53] nor Friedlaender and Feinberg[54] observed any benefit from "benadryl" in the patients treated by them.

Urticaria appears to be the disease most amenable to treatment with antihistaminic drugs. Table 4 shows good results in 84 per cent of 334 patients treated with "benadryl" and in 79 per cent of 409 patients treated with "pyribenzamine." According both to Friedlaender and Feinberg,[54] who used "benadryl," and to Arbesman,[51] who used "pyribenzamine," the results were better in acute than in chronic urticaria. The members of the American Academy of Allergy, however, did not observe much difference.

TABLE 4.—*Results of Treatment for Urticaria*

Author	No. of Cases	Results		
		Excellent and Good		Poor
		No. of Cases	Percentage	No. of Cases
		TREATMENT WITH "BENADRYL"		
Barefoot, S. W.; Riley, K. A., and Kuhn, B. H.: Am. J. Med. 3:309, 1947	19	16	84	3
Curtis, A. C., and Owens, B. B.: Arch. Dermat. & Syph. 52:239 (Oct.) 1945	18	14	177	4
Friedlaender (Footnote 53)	12	12	00	
Various Authors	19	17	89	2
O'Leary, P. A., and Farber, E. M.: Proc. Staff Meet., Mayo Clin. 20:429, 1945	50	46	92	4
Eyermann, C. H.: J. Allergy 17:210, 1946	14	13	95	1
Friedlaender and Feinberg (Footnote 54)				
Acute urticaria	16	14	87	2
Chronic urticaria	14	10	71	4
Waldbott (Footnote 48)	20	16	80	4
Levin (Footnote 52)	11	8	72	3
McGavack, Elias and Boyd (Footnote 47)	36	33	92	3
Wagner (Footnote 49)	46	34	74	12
Bernstein, Rose and Feinberg (Footnote 42)	30	24	80	6
Blumenthal, L. S., and Rosenberg, M. A.: J.A.M.A. 135:20 (Sept. 6) 1947	29	24	82	5
Total for "benadryl"	334	281	84	53 (16%)
		TREATMENT WITH "PYRIBENZAMINE"		
American Academy of Allergy (Footnote 50)				
Acute urticaria	121	94	77	27
Chronic urticaria	97	76	78	21
Arbesman, Koepf and Lenzner, (Footnote 51)				
Acute urticaria	47	44	93	3
Chronic urticaria	107	84	78	23
Bernstein, Rose and Feinberg (Footnote 42)	37	28	78	9
Total for "pyribenzamine"	409	326	79	83 (20%)

52. Levin, S. J.: β-Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl): Its Use in Allergic Diseases, J. Allergy **17**:145, 1946.

53. Friedlaender, A. S.: The Use of a Histamine Antagonist, Beta-Dimethylaminethyl Benzhydryl Ether Hydrochloride in Allergic Disease, Am. J. M. Sc. **212**:185, 1946.

54. Friedlaender, S., and Feinberg, S. M.: Histamine Antagonists: III. The Effect of Oral and Local Use of β-Dimethylaminoethyl Benzhydryl Ether Hydrochloride on the Whealing Due to Histamine Antigen-Antibody Reactions, and Other Whealing Mechanisms; Therapeutic Results in Allergic Manifestation, J. Allergy **17**:129, 1946.

54a. Through error, footnote numbers 55 to 63 were allowed for references which have been incorporated in table 4.

Summary of Clinical Results.—Taken together (table 5), the figures available so far indicate that "pyribenzamine," with good results in 64 per cent of nearly 2,000 cases, is a little more effective than "benadryl," with good results in only 61 per cent of 1,341 cases. A paper by Rose and his co-workers[63] from Feinberg's laboratory shows that in guinea pig anaphylaxis, "benadryl" gives greater protection against shock than does "pyribenzamine." In an interesting work on asthma experimentally produced in human beings by histamine aerosol, Curry[64] observed that "benadryl" given intravenously produced remarkably rapid protection against histamine, whereas "pyribenzamine" given by mouth produced a much slower protective effect. He recognized that the two drugs were not tested by the same method. In a recent paper, Loveless[65] has also made a comparative study of the literature on the clinical effects of "benadryl" and "pyribenzamine." Her report gives many details omitted here, but her gross figures are comparable. More comparative studies on the clinical effects of these drugs are needed. The few comparative observations which have been made in the laboratory will be noted later.

Untoward Effects of the Antihistaminic Drugs. These are reviewed in the paper by Loveless. Sedation, or drowsiness, observed in 43 per cent of the patients treated with "benadryl," occurred after administration of "pyribenzamine" in only 8.5 per cent. Gastrointestinal disturbances

TABLE 5.—*Summary of Results*

	Results with "Benadryl"			Results with "Pyribenzamine"		
	Total No. of Patients Treated	Good Results		Total No. of Patients Treated	Good Results	
		No. of Patients	Percentage		No. of Patients	Percentage
Hay Fever	446	291	65	619	481	77
Vasomotor rhinitis	165	84	51	545	347	63
Asthma	396	166	42	417	137	33
Urticaria	334	281	84	409	326	79
Total	1,341	822	61	1,990	1,291	64

63. Rose, J. M.; Feinberg, A. R.; Friedlaender, S., and Feinberg, S. M.: Histamine Antagonists: VII. Comparative Antianaphylactic Activity of Some New Antihistaminic Drugs, J. Allergy **18**:149, 1947.

64. Curry, J. J.: The Effect of Antihistamine Substances and Other Drugs on Histamine Bronchoconstriction in Asthmatic Subjects, J. Clin. Investigation **25**: 792, 1946.

65. Loveless, M. H.: Therapeutic and Side Effects of Pyribenzamine and Benadryl: Comparative Study Based upon a Survey on Twenty-Six Clinical Reports in the Literature, Am. J. Med. **3**:296, 1947.

occurred equally in the two series in about 8 per cent of the cases. Excitement, "jitters," insomnia and palpitation occurred in 10 per cent of the patients treated with "benadryl," but in only 3 per cent of the patients treated with "pyribenzamine." Dizziness was observed in 7 per cent after treatment with "benadryl" and in 3 per cent after treatment with "pyribenzamine." There were still other symptoms in a few cases.

A few other and special reports are interesting. Slater and Francis[66] describe the case of a truck driver who took a 50 mg. capsule of "benadryl" for his hay fever and two hours later went to sleep at the wheel. Children particularly show side reactions, varying from drowsiness to vomiting. Levin[52] observed them in 63 per cent of his 223 patients treated with "benadryl." McGavock and his associates[47] observed them in over half their cases. Using "pyribenzamine," Arbesman and his coworkers[51] observed side effects in 144 of 495 patients, or 29 per cent. It is true that in only 22 of these were the side effects severe, and the authors declare that danger from the drugs is not great, that disturbing symptoms may occur, but they pass off. Nevertheless, Geiger, Rosenfield and Hartman[67] report the case of a young woman, aged 26, with generalized seborrheic dermatitis, who was given 300 mg. of "benadryl" in the course of three days and then suddenly was found unconscious, cold, pale and pulseless. After the administration of epinephrine she revived.

Leukopenia and granulocytopenia has been observed to follow administration of the antihistaminic drugs, as they have followed administration of other drugs of complicated chemical structure. Cole of Cleveland[68] wrote me in November 1946: "I have known granulocytopenia to occur in several cases following the use of 'benadryl'." Blanton and Owens[69] describe a woman of 73 who had urticaria for seven weeks and was given "pyribenzamine," 200 mg. each day. She improved, and treatment with the drug was continued, 160 mg. each day. Twenty-five days later the symptoms recurred; her temperature rose to 103 F., and her white blood cell count fell to 1,300, with only 3 per cent polymorphonuclear leukocytes in the smear. Feinberg[34] ends his report with the note that "the remote toxicity from these drugs has not been sufficiently ascertained up to this time."

My results agree with those in the reports in the literature. In the summer of 1947, 82 patients with hay fever due to ragweed, who still

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66. Slater, B. J., and Francis, N.: Benadryl: A Contributing Cause of an Accident, J. A. M. A. **132**:212 (Sept. 28) 1946.

67. Geiger, J.; Rosenfield, S. Z., and Hartman, D. L.: Unusual Reaction Following Benadryl Administration, J. A. M. A. **133**:392 (Feb. 8) 1947.

68. Cole, H. N.: Personal communication to the author.

69. Blanton, W. B., and Owens, M. E. B., Jr.: Granulocytopenia Due Probably to "Pyribenzamine," J. A. M. A. **134**:454 (May 31) 1947.

had symptoms in spite of specific treatment, were given "benadryl" in average doses of 200 mg. a day. Of this group, 55, or 67 per cent, felt that the drug was helpful. Side effects were common, especially drowsiness, and some patients said that the hay fever itself was less troublesome than these side effects. The doses taken are variable, and this fact makes all reports of the specific effect irregular and difficult to compare. The practical point which develops from this is that the clinical use of any of these drugs requires careful attention to dosage. Whereas the 50 mg. capsule or tablet may cause drowsiness, if at the same time it relieves the sneeze or the itch, one may observe that half the quantity, or 25 mg., given only once or twice a day, especially at bedtime, will also provide relief, yet without producing symptoms which are disagreeable. The drowsiness will do good rather than harm. The sedative effect can be utilized as an advantage in place of a disadvantage. In children, and in adults too, even smaller quantities can be given if the drug is prescribed as a liquid mixture, of which a teaspoonful contains only 10 mg.

Other drugs in this series, in addition to "antergan" and "neoantergan," will be developed and marketed soon. They will be useful as adjuncts to the older methods of treatment, but they will not replace them.

Comment.—Since the principles which led to the development of these drugs are sound, it is proper to consider various reasons for the disappointing clinical effect. There are two main questions: First, are the drugs truly antihistaminic? Do they neutralize histamine in animals? Do they inhibit the known effects of histamine in human beings? Second, is histamine the cause of symptoms in each case, or can one say that different types of asthma, for example, have different mechanisms?

ARE THE NEW DRUGS TRULY ANTIHISTAMINIC?

As to the first question, the shock which follows the intravenous injection of histamine into guinea pigs can be prevented by previous treatment of the animals with antihistaminic drugs. Friedlaender, Feinberg and Feinberg[70] observed that animals treated with "benadryl" in doses of 3 mg. per kilogram of body weight could tolerate five lethal doses of injected histamine and that other animals treated with "pyribenzamine," 3 mg., could tolerate thirty-seven lethal doses. In the same experiment "antergan" was observed to protect against six lethal doses, while "neoantergan" injected in the same quantity could protect against one hundred and twenty-five lethal doses.

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70. Friedlaender, S.; Feinberg, S. M., and Feinberg, A. R.: Histamine Antamine Antagonists: V. Comparative Study of Benadryl and Pyribenzamine in Histamine and Anaphylactic Shock, Proc. Soc. Exper. Biol. & Med. **61**:65, 1946.

Asthma may be experimentally induced in guinea pigs by exposing them to a spray of histamine aerosol. Loew and his associates[71] studied the protective effect of a number of compounds injected intraperitoneally fifteen minutes before the time of exposure to the spray and observed that all of the drugs protected in some degree. If the effect of aminophylline was 1, "benadryl" had an activity of 33. For comparison, although the mechanism of its action is different, epinephrine had an activity of 500. Mayer[72] observed that, whereas the histamine aerosol killed normal guinea pigs in about two and a half minutes, pretreatment of the animals with a single dose of "pyribenzamine," 0.10 mg. per kilogram of body weight, injected subcutaneously was enough to protect the animals unless the drug was given more than four hours before the test.

Experiments on the isolated muscle suspended in the Dale bath are even more direct. Loew and his co-workers[73] observed that "benadryl" was active in preventing the contraction when it was added to the bath in high dilution (1 to 25,000,000) just before the minimum effective dose of histamine (also in high dilution, 1 to 125,000,000). Mayer[72] observed that "pyribenzamine" was also effective: the addition of as little as 0.02 gamma per cubic centimeter (1 to 5,000,000) to the Dale bath neutralized as much as 1.0 gamma per cubic centimeter of histamine (1 to 1,000,000).

Loew and his co-workers[73] brought out the important point that "benadryl" can inhibit the contraction of the muscle strip when it is stimulated not only by histamine but also by such diverse substances as barium chloride and acetylcholine. The doses, however, are important. Against histamine, "benadryl" is effective in a dilution of 1 to 25,000,000 or 50,000,000, whereas against barium chloride a dilution of 1 to 10,000 was required. Against acetylcholine, "benadryl" is effective in a dose of 1 to 8,000,000, in contrast to atropine, which is effective in a concentration of 1 to 100,000,000. As the authors point out, the atropine-like qualities are increased at the expense of the antihistaminic effect. This atropine-like effect suggests that "benadryl" has an effect on the smooth muscle cells, or perhaps on the neuroeffector mechanism, which is in addition to its effect on histamine. However, this other property of "benadryl" requires much larger amounts for its effect, and Loew concludes that "benadryl" is essentially a specific inhibitor of histamine.

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71. Loew, E. R.; Kaiser, M. E., and Moore, V.: Effect of Various Drugs on Experimental Asthma Produced in Guinea Pigs by Exposure to Atomized Histamine, J. Pharmacol. & Exper. Therap. **86:1**, 1946.

72. Mayer, R. L.: Antihistaminic Substances with Special Reference to Pyribenzamine, J. Allergy **17:153**, 1946.

73. Loew, E. R.; MacMillan, R., and Kaiser, M. E.: The Antihistaminic Properties of Benadryl 6-Dimethylaminoethyl Benzhydryl Ether Hydrochloride, J. Pharmacol. & Exper. Therap. **86:229**, 1946.

Direct comparisons between the effect of the drug against histamine and the effect against the antigen-antibody reactions of anaphylaxis have been made. Yonkman and his associates[74] removed the lungs from guinea pigs sensitized to horse serum and perfused the organs by injecting isotonic solution of sodium chloride through the trachea, collecting the perfusate as it escaped from scratches made in the pulmonary surface. When the specific antigen-horse serum was added to the perfusion fluid, the escape of perfusate dropped off sharply. Bronchospasm was apparent. When, however, "pyribenzamine" was added to the perfusion fluid ten or twenty minutes before the horse serum, no change in the rate of perfusion occurred. The bronchospasm did not occur. When the lungs were perfused with histamine, it was observed that "pyribenzamine," added just before the test, could inhibit the normal resistance to the passage of fluid; this time the bronchospasm was prevented. The protection supplied by "pyribenzamine" against histamine, but not against the specific foreign serum reactions, is difficult to explain, especially as in anaphylactic shock in the whole animal "pyribenzamine" affords such good protection.

Rose and his co-workers,[75] using a different technic, did not come to all of the same conclusions. They observed that each of the antihistaminic drugs protected against anaphylactic shock in the guinea pig, and the fact that this protection diminished as the dose was decreased was considered as evidence that the shock was dependent on the release of histamine. On sensitized muscle strips, the drugs were effective against the anaphylactic contractions, and, more than that, the dose which was effective in that experiment was not enough to protect against a contraction of the same magnitude due to histamine. In explanations of the discrepancy that the drug can inhibit the reaction of the muscle strip sensitive to antigen better than it can inhibit the reaction of the normal strip to histamine, the authors point out that in active sensitization the histamine is in closer contact with the muscle cells, and this may be so. I, however, am skeptical of the premises, because the authors did not study the minimum quantity of histamine which could have produced a contraction "of that magnitude."

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74. Yonkman, F. F.; Oppenheimer, E.; Rennick, B., and Pellett, E.: Pharmacodynamic Studies of a New Antihistaminic Agent, Pyribenzamine (N, N-Dimethyl-N-Benzyl-N-[*a*-Pyridyl]-Ethylene Diamine Hydrochloride): II. Effects on Smooth Muscle of the Guinea Pig and Dog Lung, J. Pharmacol. & Exper. Therap. **89**:31, 1947.

75. Rose, J. M.; Feinberg, A. R.; Friedlaender, S., and Feinberg, S. M.: Histamine Antagonists: VII. Comparative Antianaphylactic Activity of Some New Antihistaminic Drugs, J. Allergy **18**:149, 1947.

Halpern[76] has studied several new antihistaminic drugs. Each of these was effective in protecting the isolated muscle strip against histamine, and each prevented the development of asthma in guinea pigs after the administration of histamine aerosol. Substance "3015 R.P." (N-dimethylaminoethyl-thiodiphenylamine) protected a guinea pig against four hundred lethal doses of injected histamine, whereas "antergan" protected against only sixty doses. Against anaphylactic shock, however, 5.0 mg. per kilogram of body weight of "3015 R.P." was required, whereas only 1.0 mg. per kilogram of body weight of "antergan" was sufficient. Another substance, "3277 R.P." (N-dimethylamino-2-propyl-1-thiodiphenylamine), protected against anaphylaxis in a dose as small as 0.50 mg. per kilogram of body weight, and the standard quantity could protect the guinea pig against fifteen hundred lethal doses of injected histamine. This second substance, therefore, is ten times as active against histamine. As Halpern concludes: "One is obliged to recognize that the antianaphylactic shock action of this series of substances does not run parallel with their antihistaminic activity."

Cutaneous tests, intradermal injections of various substances, were done on rabbits by Last and Loew.[77] Pretreatment of the animals with "benadryl" or "neoantergan" blocked the reactions to the test with histamine, but had no effect on the reactions to intradermal injections of trypsin, snake venom or codeine in normal animals, and, more important, there was no effect on the reaction to horse serum in sensitized rabbits. This last is in contrast to the effect in allergy in human beings, in whom, as will be shown, pretreatment tends to inhibit the specific cutaneous reaction.

The effect on the stomach of dogs and the effect on mice is interesting. It suggests a synergistic action of "benadryl." When "benadryl" in wax and histamine in wax were given simultaneously and daily to 7 dogs, gastric and/or duodenal ulcerations developed in all, according to Friesen, Baronofsky and Wagensteen.[78] Mice were treated by Mayer and Broussea[79] with a mixture of "pyribenzamine or "benadryl" and histamine, and the animals died from doses which were smaller than the doses used when each drug had been given separately.

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76. Halpern, B. N.: Experimental Research on a New Series of Chemical Substances with Powerful Antihistaminic Activity: The Thiodiphenylamine Derivatives, J. Allergy **18**:263, 1947.

77. Last, M. R., and Loew, E. R.: Effect of Antihistamine Drugs on Increased Capillary Permeability Following Intradermal Injections of Histamine, Horse Serum and Other Agents in Rabbits, J. Pharmacol. & Exper. Therap. **89**:81, 1947.

78. Friesen, S. R.; Baronofsky, I. D., and Wagensteen, O. H.: Benadryl Fails to Protect Against Histamine-Provoked Ulcer, Proc. Soc. Exper. Biol. & Med. **63**:23, 1946.

79. Mayer, R. L., and Broussea, D.: Antihistaminic Substances in Histamine Poisoning and Anaphylaxis of Mice, Proc. Soc. Exper. Biol. & Med. **63**:197, 1946.

In human beings simple experiments show the antihistaminic effect of these drugs. That histamine will produce a typical wheal-erythema reaction to a cutaneous test is well known. Friedlaender and Feinberg[54] gave 50 mg. of "benadryl" by mouth three times a day for a week, and then made cutaneous tests with histamine in normal persons as well as with the specific antigen in allergic patients. With this dose, there was no change in the subsequent cutaneous reactions, but, when the dose was increased to 100 mg. and given one hour before the test, the reactions were milder after than before the treatment with the drug, but the eruptions did not disappear. When the drug was mixed in the test tube with the histamine or the antigen beforehand, the cutaneous reactions were reduced in all instances.

Cohen and his co-workers[80] gave their patients "benadryl," 50 mg. four times a day, and then made cutaneous tests with dilutions of histamine, by the method of iontophoresis. Their subjects were protected against an average of eight times the whealing dose. They also made cutaneous tests with mixtures of histamine and "benadryl," but, unlike the previous investigators, they could not demonstrate that "benadryl" prevented the usual histamine response. Arbesman and his coworkers[81] have also studied wheals due to histamine and observed that "pyribenzamine" given by mouth in doses of 50 to 150 mg., and taken forty-five minutes before the cutaneous tests were repeated intradermally with histamine dilutions, caused a decrease in both histamine and allergic wheals in about two thirds of the cases. More recently McGavack and his co-workers[47] repeated Friedlaender's experiments on whealing, and their results were irregular.

The specific effect of histamine on the gastric secretions offers another means of studying the antihistaminic effect. Loew and his coworkers[73] observed that "benadryl" inhibits from 40 to 80 per cent of the normal response in human beings.

In summary, in answer to the first question "benadryl" and "pyribenzamine" can neutralize histamine both in animals and in human beings, and this effect is specific. In human beings, on the other hand, as in anaphylaxis and in experiments involving antigen-antibody reactions, the effects of the drugs are rather irregular.

IS HISTAMINE THE CAUSE OF SYMPTOMS IN EACH CASE?

In answer to the second question, whether the irregular results in the use of these drugs can throw any light on the mechanisms of allergic

80. Cohen, M. B.; Friedman, H. J.; Zomis, J.; Burke, M., and Abram, L. E.: The Effect of Beta-Dimethylaminoethyl-Benzhydryl-Ether-Hydrochloride on the Histamine Threshold of Human Skin, J. Allergy **18**:32, 1947.

81. Arbesman, C. E.; Koepf, G. F., and Miller, G. E.: Some Antianaphylactic and Antihistaminic Properties of N'Pyridyl, N'Benzyl Dimethylenediamine Monohydrochloride (Pyribenzamine), J. Allergy **17**:203, 1946.

diseases, the drugs are not so effective in asthma as they are in hay fever and urticaria. It is possible that this difference indicates a different mechanism in different cases, but so far there are no data to support such a thesis. Wagner[49] observed that "benadryl" was twice as effective in asthma which was seasonal as it was in asthma which was intrinsic, but Waldbott[48] saw no such distinction. It is fair to point out that even in hay fever, which appears to be a uniform disease with a simple and well defined cause, the results vary between 52 and 94 per cent, and the best average is not more than 77 per cent. If now the results in hay fever are so far from uniform, what use is there to speculate on the irregularities in asthma? The one fact that the drugs are not 100 per cent effective is important. It suggests that histamine is not the only mechanism for symptoms. There is probably a fallacy in this argument which depends on the difficulty of appraising the clinical results. Is it likely that each author used the same dosage and continued the use of the drug for the same number of days in each patient? Was he careful to include in his report only those patients who had received minimum treatment, and what was this minimum? Did the untoward reactions make many patients give up treatment with the new drug? Is it not probable that a more critical study would yield a better correlation of the results?

Meantime, Loew[35] reports other actions of antihistaminic drugs: in anesthetized animals they stimulate respiration, with depression later. Blood pressure may fall at first and rise later; the changes are not too perceptible. The drugs prevent histamine from relaxing the smooth muscle of systemic arterioles and coronary vessels. They have some local anesthetic action. Large doses in animals will cause hyperexcitability, with tremor and convulsions. The effectiveness of the drugs in anaphylaxis and allergy depends on their ability to block the effects of histamine on smooth muscle, both vascular and visceral.

The second question, therefore—whether histamine is the cause of symptoms in each case—can be answered only by saying that the evidence at hand suggests that, since the antihistaminic drugs are so much more active against histamine than they are against allergic reactions, the latter are due to factors other than, or in addition to, histamine. Sir Thomas Lewis was wise to designate the intermediary factor as "H substance," and for the present it is best to retain that broad and all-inclusive designation.

Whether further study of the free histamine in the blood plasma will show that it varies directly with the severity of symptoms is perhaps doubtful, but the question should be answered. On the whole, the case for histamine itself, as the mediating factor in allergic disease, is not good enough. Must consideration be limited to the filtrate which remains when the blood sample is boiled with acid? The clinician is

obliged to think of an active substance or principle which arises in the body, often rather suddenly, from a variety of exciting factors: from allergic reactions in young patients, but from infections of various kinds, and from the vague disturbances of somatic and of psychic depletion, or stress and strain, in the older patients. There is no doubt about the acute suffering which ensues. The symptoms suggest "poisoning" of some sort. They are relieved by treatment with epinephrine, aminophylline and, especially, fluid given in quantity intravenously, but the antihistamine drugs are not good enough for them. What are the other possible mediators?

Selye[82] describes the adaptation syndrome as an explanation of the characteristic group of symptoms (systemic reactions) which develop from stress, and the stress includes the effect of noxious agents in considerable variety. Physical injuries—wounds, fractures and burns—excite the "alarm reaction," which is the first part of the syndrome, but injuries which are less violent, like cold or anorexia from high altitude, can do it, as well as poisonings from drugs and chemicals. Most important to me, the concept includes the idea that fatigue and the stress and strain from emotional factors can produce the same syndrome. I believe that Selye's theory is plausible. The pathologic changes which he has described, and which will be noted later, are comparable to the changes seen in allergic disease. So far Selye has not considered the release of histamine or other hormone as the mediating substance in his syndrome. Rose, however, has studied the matter. In experiments not yet published, he was unable to demonstrate any significant change in the histamine in the blood in rats during various stages of the "alarm reaction." Selye's theory is that the reactions depend on changes in the secretion of the adrenal cortex, or rather in the corticotropic hormones from the pituitary which stimulate the adrenal cortex to produce its hormones with their three general functions: the 17 ketosteroids, including the testoid hormone, the salt-active corticoids, like desoxycorticosterone (a synthetic compound of the adrenal cortex), and the sugar-active corticoids. (Selye is discussed again in part II, under "Pathologic Changes.")

Forbes points out that Forsham and his co-workers,[82a] Bartter and his co-workers[82b] and others have produced "alarm reactions" in human

82. Selye, H.: The Alarm Reaction, in Piersol, G. M., and Bortz, E. L.: Cyclopedia of Medicine, Surgery and Specialties, ed. 2, Philadelphia, F. A. Davis Company, 1940; Diseases of Adaptation, J. Allergy **17**:231, 289 and 358, 1946; General Adaptation Syndrome and Diseases of Adaptation, J. Clin. Endocrinol. **6**:117 1946.

82a. Forsham, P. H.; Thorn, G. W.; Prunty, F. T. G., and Hills, A. G.: Clinical Studies with Pituitary Adrenocorticotropin, J. Clin. Endocrinol. **8**:15, 1948.

82b. Bartter, P.; Albright, F., and Forbes, A. P., in Conference on Metabolic Aspects of Convalescence, New York, Josiah Macy Jr. Foundation, 1945.

subjects by injecting pituitary adrenocorticotropic hormone. There was diuresis of potassium, calcium and phosphorus, with retention of sodium. There was loss of nitrogen and uric acid and increase of the polymorphonuclear white cells, with decrease in the lymphocytes and disappearance of the eosinophils. There was elevation of the blood pressure in 1 case. Whether further study will show that these features will occur in asthma remains to be seen. Since the 17-ketosteroid excretion has been observed to be lower than normal in patients with asthma, Forbes suggests the possibility that in these patients, because of exhaustion of the adrenal gland by repeated alarms, the usual healthy reaction to stress may be altered.

In the meantime, patients are conditioned for the development of "allergic disease." Other patients suffer the same sort of infections and the same sort of stress and strain, but arthritis develops in place of asthma, presumably because they are conditioned that way, because they were born with a "Y" instead of an "X" factor. This is another vital problem. Is there an approach to it?

PART II. PATHOLOGIC ASPECTS, DIAGNOSIS AND TREATMENT

Several good books on allergy appeared in 1946 and 1947. The second edition of a large volume entitled "Allergy," by Urbach and Gottlieb,[83] is indeed a complete work. It has nine hundred and sixty-eight large pages, with two columns to the page. It covers every phase of the subject; it refers to almost every paper which bears on allergic disease that has been writen in recent years.

The second edition of Feinberg's "Allergy in Practice"[84] also appeared in 1946. This book is complete, if not so all-inclusive. It has eight hundred and thirty-eight pages, but they are of average size and more readable than those of the first edition. More important, the author is critical and selects his references with care. His discussion is complete and sound. Many chapters have over a hundred references listed at the end. Important topics are given the relatively more attention which they require.

"The Diagnosis and Treatment of Bronchial Asthma" by L. H. Gay[85] is a smaller book. Its three hundred and thirty-four pages deal with asthma only, and the discussion is built up around a great number of reports of cases. It is a clinical study and makes interesting reading. The author does not attempt to elaborate on the physiologic and immunologic aspects of the disease, but the pathologic aspects of asthma are

83. Urbach, E., and Gottlieb, P. M.: Allergy, ed. 2, New York, Grune & Stratton, Inc., 1946.

84. Feinberg, S. M.; Durham, O. C., and Dragstedt, C. A.: Allergy in Practice, ed. 2, Chicago, The Year Book Publishers, Inc., 1946.

85. Gay, L. N.: The Diagnosis and Treatment of Bronchial Asthma, Baltimore, Williams & Wilkins Company, 1946.

described well. The book reflects the author's wide experience in the clinic at Johns Hopkins Hospital.

The "Treatment of Bronchial Asthma," by Derbes and Engelhardt,[86] is a moderate volume of four hundred and sixty-six pages. It is not a monograph, like the books mentioned; it is a compendium, with the different chapters written by different authors. The editors, however, have written eight of the twenty-three chapters. The emphasis is on cutaneous tests, and on the description of allergenic substances, pollens, dusts and foods. There is an interesting chapter, "Anatomy and Physiology of the Respiratory Tract," by G. E. Burch of Tulane University, but the chapter on immunology, by M. B. Cohen, is too much simplified.

Cooke's "Allergy in Theory and Practice"[87] is also a compendium, but Cooke himself has written twelve of the thirty-two chapters, as well as the appendix. There are five hundred and seventy-two pages. The principles and theories of allergy are discussed in able fashion, and opposing views are described. There are one or two unnecessary pictures, but there is none of the padding by photographs of plants, pollens and cutaneous lesions which have appeared elsewhere. Every student of allergy needs this book.

PATHOLOGIC ASPECTS OF ALLERGIC DISEASE (RICH AND SELYE)

The pathologic aspects of allergic disease are becoming more understood, chiefly because of studies under way in the laboratories of Rich[88] of Johns Hopkins University and Selye[82] of Montreal, Canada. That this is a new development is shown by the short treatment in the textbooks just described. The enormous work of Urbach and Gottlieb devotes only three pages to the pathologicoanatomic aspects of allergy with the histologic aspects of allergic reactions. In another section, however, vascular lesions, including periarteritis nodosa, receive better treatment. Feinberg treats symptoms and pathologic changes together with periarteritis, which appears at the end of the book under miscellaneous topics. Gay, dealing with asthma, describes the pathologic aspects of asthma, giving many reports of cases and tables. Periarteritis is described. Derbes and Engelhardt describe the clinical pathologic aspects.

In Cooke's book is Klemperer's[89] discussion of the pathologicoanatomic aspects of allergy. First of all, there is no one lesion which is produced in the antigen-antibody reaction and in no other injury. The outpouring

86. Derbes, V. J., and Engelhardt, H. T.: The Treatment of Bronchial Asthma, Philadelphia, J. B. Lippincott Company, 1946.

87. Cooke, R. A.: Allergy in Theory and Practice, Philadelphia, W. B. Saunders Company, 1947.

88. Rich, A. R.: The Significance of Hypersensitivity in Infections, Physiol. Rev. 21:70, 1941.

89. Klemperer, P.: Pathologic-Anatomic Aspects of Allergy, in Cooke,[87] p. 69.

of eosinophils is characteristic, but it is not specific. The problem is complex because of the two phases of the reaction. When foreign protein meets its specific antibody on the surface of the tissue cell, the typical response is an immediate wheal and erythema reaction. In mild reactions there is local edema with moderate infiltration of cells, many of which are eosinophils, but in severer reactions the process involves the endothelium of blood vessels and involves the collagen to produce fibrinoid degeneration of the connective tissue. The so-called Arthus phenomenon, with necrosis resulting primarily from the damage to the blood vessels, represents the end stage. It is produced most easily in the skin of the sensitized rabbit, but it may occur in other tissues and in other animals also. As Zinsser[90] showed originally, this immediate reaction requires a high concentration of antibodies, and thus this special kind of inflammatory reaction represents the late stage of the allergic process. The tuberculin reaction is different. It is "allergic" because it also requires the participation of factors in the tissue of the host. However, it requires less antibodies and so may often be elicited in the early phase of the process, before the animal is "ready" for the reactions of the immediate type. This reaction appears twenty-four hours after the last dose; it is delayed. Whereas Dienes and Mallory[91] described certain histologic differences between the immediate and the delayed types of response, Klemperer states that in strong reactions the difference is not evident. Meantime, the whole problem of bacterial allergy is complicated by the primary toxicity of bacteria and their products, which cause changes without the aid of the host-tissue factor.

The studies made by Rich[88] and by Selye[82] have advanced knowledge greatly. The concept of the pathogenesis of the allergic diseases has been broadened: First, the background of such allergic manifestations as asthma and eczema has been improved by the better understanding of the basic reactions involved. Second, similar reaction patterns have been seen in other diseases, so that allergy is recognized as a factor in the pathogenesis of such diseases as rheumatic fever and perhaps glomerulonephritis. Other conditions in which the histologic observations include fibrinoid degeneration of the colloid may turn out to depend on a mechanism which includes allergic reactions. Thromboangütis obliterans, lupus eythematosus, scleroderma and perhaps interstitial nephritis may be studied from this new viewpoint. The variety of acute endocarditis which is nonbacterial and is called Libman-Sacks disease, from its original describers,[92] is in the same group. To include these

90. Zinsser, H.: Studies on the Tuberculin Reaction and on Specific Hypersensitiveness in Bacterial Infection, J. Exper. Med. **34**:495, 1921.

91. Dienes, L., and Mallory, T. P.: Histological Studies of Hypersensitive Reaction, Am. J. Path. **8**:689, 1932.

92. Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Arch. Int. Med. **33**:701 (June) 1924.

obscure conditions in the allergic concept at this time is somewhat bold, but at least the idea is interesting. How did it come about?

Periarteritis Nodosa (Loeffler's Syndrome).—In 1942 Rich[93] observed 7 patients who died and who had presented a clinical syndrome like that of serum disease. They had fever and prostration, but the typical symptom was a diffuse urticarial rash which suggested poisoning of some sort. At autopsy in 4 of the cases, the typical lesions of periarteritis nodosa were shown—the familiar picture of necrosis with fibrinoid degeneration, hyalinization, hemorrhage and eosinophilia. Rich pointed out that this type of disease was new; it had appeared during the year when sulfonamide drugs were first used in large doses and in many patients, and the first question was whether the illness and the characteristic pathologic changes depended on the primary infection which had made the patient ill in the first place or whether it was the serum used in treatment or the sulfonamide drug, or a combination of these three factors.

In the meantime, other workers, starting with Kussmaul and Maier[94] in 1866, have described periarteritis nodosa in character, if not in name, and the condition did occur occasionally in patients treated with large doses of foreign serum. In 1943 Rich and Gregory[95] selected 14 large rabbits; into 9 of them was injected horse serum in doses of 10 cc. per kilogram of body weight, an enormous quantity. Five of the rabbits received, in addition, sulfadiazine in doses of 0.5 Gm. per kilograms of body weight. On the twelfth day cutaneous tests showed that all the rabbits were hypersensitive to horse serum, and on the seventeenth day all were inoculated with 1 cc. of horse serum. Two of the animals died, and later the others were killed. At autopsy every stage of periarteritis nodosa could be seen in these rabbits. It was obvious that the blood vessels had become the seat of severe anaphylactic injury. Later, it was observed that one large dose of serum was enough to cause the lesions and that the addition of sulfadiazine was not essential in producing the injury to the blood vessels. As expected, the kidneys of these animals showed severe focal lesions of the glomeruli; the process of allergy is evidently concerned with the pathologic changes of glomerulonephritis.

The lesion is comparable to the lesion of the Arthus phenomenon and is different from the lesion observed in reactions to bacteria of the tuberculin type. Before the Academy of Allergy, in December 1945,

93. Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, Bull. Johns Hopkins Hosp. **71**:123, 1942.

94. Kussmaul, A., and Maier, R.: Periarteritis Nodosa, Deutsches Arch. f. klin. Med. **1**:484, 1866.

95. Rich, A. R., and Gregory, J. E.: The Experimental Demonstration that Periarteritis Nodosa Is a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. **72**:65, 1943.

Scherp[96] reviewed the differences between the Arthus reaction and the tuberculin reaction. The Arthus reaction depends on vascular damage, as Rich demonstrated. The tuberculin reaction, however, depends on the destruction of sensitized cells near, but outside, the blood vessels. Circulating antibody is important for the Arthus reaction, and its severity depends on the concentration of these antibodies. The tuberculin reaction, however, is also a specific phenomenon; the animal reacts only when treated with the organism which primarily sensitized it, and antibodies are necessary, but the point is that these antibodies are attached to the cells and are not free in the circulating blood. The subject is discussed well by Rich[88] in his paper in *Physiological Reviews* (1941). In that paper the significance of hypersensitivity in infections is discussed. More recently Rich has pointed to the fact that, whereas before sulfonamide drugs came into general use only 6 cases of periarteritis nodosa had been seen at the Johns Hopkins Hospital, since then 32 cases have been discovered. Also, the localized lesions, called "Aschoff bodies," seen in rheumatic carditis have a periarterial location, which makes them comparable to the lesions in periarteritis nodosa, and that, in turn, identifies them as another manifestation of allergy. A useful review of this subject is in a recent paper by Bohrod.[97]

Selye[82] also has produced the lesions of periarteritis nodosa, but by a different principle. "Desoxycorticosterone," the salt-active corticoid of the adrenal cortex, when given in large doses to normal animals, will give rise to vascular lesions identical with those seen in periarteritis nodosa, to myocardial and joint lesions similar to those in rheumatic fever, to nephrosclerosis and sometimes to acute nephritis. This occurs more intensively when large amounts of sodium chloride are given by mouth at the same time. There is a retention of sodium and a loss of potassium, but the latter is not important, for the addition of potassium chloride does not prevent the lesions. On the other hand, the ammonium salts, chloride and sulfate, will protect the animal against the effect of "desoxycorticosterone," perhaps because the elimination of sodium is enhanced. The pictures in Selye's paper show well that lesions of many organs occurred in the animals treated either with anterior pituitary material containing the corticotropic hormone or with "desoxycorticosterone acetate," and salt. Foci and arterial lesions in the myocardium, ulcerations in the stomach, thrombi in the mesentery, arterial lesions in the brain, glomerular lesions in the kidney and inflammation of the joints are all depicted.

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96. Scherp, H. W.: Hypersensitivity to Infectious Agents in Relation to Asthma, J. Allergy **17**:255, 1946.

97. Bohrod, M. G.: Classification of the Histologic Reactions in Allergic Diseases, Am. J. Med. **3**:511, 1947.

Comparison of the works of Rich and Selye is interesting. Rich produced periarteritis with sulfonamide drugs in the presence of infection and also with foreign serum in large doses. Selye produced the same type of lesions with a glandular extract and more pronounced lesions with the addition of salt. Several questions arise: Is an antigen-antibody reaction essential? Does Selye's "desoxycorticosterone" produce antibodies to itself? Selye and Pentz[98] have demonstrated that periarteritis can be produced by a variety of nonspecific damaging agents, including exposure to cold. This last is important because it encourages the idea that in patients with asthma it is not necessary to consider an antigen-antibody reaction, an allergy in each case; the concept of depletion resulting from stress and strain is evidently satisfactory, provided only that asthma be considered as one of the "diseases of adaptation."

If this is true, why is periarteritis nodosa such a rare development in asthma? In 1939, Rackemann and Greene[99] described 8 patients in whom this pathologic change developed as a complication of asthma of maximum severity. Usually the lesions are not seen. Since some of the patients have recovered, it is evident that the lesions may heal of themselves, and it may be possible that under ordinary conditions they are not recognized.

An observation by Hawn and Janeway[100] is important. In studying the reactions of normal rabbits to the purified fractions of serum, they observed that it was the albumin fraction which was particularly prone to produce lesions of the arteries. Injections of beef gamma globulin caused injuries of the liver and kidneys, while involvement of the arteries generally was less conspicuous. Also, they observed that the acute lesions developed only during the time that the antigen was present in the circulating blood. As soon as the antibodies began to appear, healing of the lesions proceeded rapidly. The observations support the idea that periarteritis nodosa is a temporary process which can come and go. It may be commoner than is recognized, for recovery can occur as immunity develops and as the general condition of the patient improves.

New cases of periarteritis nodosa are reported. Contratto[101] describes a man of 40 who had pulmonary tuberculosis when he was a student. At age 34, attacks of fever and malaise developed. Small nodes were seen under the skin of his forearm; one of these was excised,

98. Selye, H., and Pentz, E. I.: Pathogenetic Correlations Between Periarteritis Nodosa, Renal Hypertension and Rheumatic Lesions, Canad. M. A. J. **49**:264, 1943.

99. Rackemann, F. M., and Greene, J. E.: Periarteritis Nodosa and Asthma, **Tr. A. Am. Physicians 54:112, 1939.**

100. Hawn, C. V., and Janeway, C. A.: Histological and Serological Sequences **in Experimental Hypersensitivity, J. Exper. Med. 85:571, 1947.**

101. Contratto, A. W.: Periarteritis Nodosa: A Report of Two Cases, One **with Special Reference to Sensitivity Factors, Arch. Int. Med. 80:567 (Nov.) 1947.**

and the lesions of periarteritis nodosa were demonstrated. He rested for a year and then went back to work, but other attacks occurred. He never was really ill. Another of the nodes, excised later, showed lesions of active tuberculosis. Ultimately the man recovered. In this case the arterial lesions were closely related to the tuberculosis. Higgins[102] reports 6 cases, demonstrating the multiplicity of pathologic and clinical manifestations characteristic of this generalized disease. Lichtenstein and Fox[103] saw typical lesions in a woman who died three weeks after an operation on her shoulder. At the time of the operation 5 Gm. of sulfathiazole had been shaken into her wound, and nine days later she experienced a sudden chill with fever and a generalized cutaneous eruption. More sulfathiazole, a quantity of 31.5 Gm., was given during the following six days, until she died. Obviously there was intoxication from too much medication in a patient who had become sensitized.

Werne and Garrow[104] report the cases of identical twins, both of whom had severe reactions following the administration of second doses of diphtheria toxoid and pertussis antigen. It is important that the first injection, given a month previously, had made the children sick with vomiting and fever, and after the second injection both were seriously ill and 1 of them died. At autopsy, lesions "consistent with anaphylactic shock" were demonstrable, but more important, a series of vascular lesions seen in all the organs made a characteristic picture of periarteritis nodosa. I noted that in each of these "new cases" an antigen-antibody mechanism could be considered as operative. Other cases without this mechanism should be found.

Loeffler's syndrome, transitory infiltrations of the lungs, may come and go with surprising speed. Wright and Gold[105] observed the roentgen shadows to come and go in patients with creeping eruption due to cutaneous helminthiasis; 4 cases were reported by Blanton.[106] Henderson and Pierce[107] point out that the diagnosis of Loeffler's syndrome requires that roentgenograms of the chest be taken at frequent intervals. Herbut

102. Higgins, W. H.: Periarteritis Nodosa: Clinical Manifestations and Postmortem Findings with a Report of Six Cases, South. M. J. **39**:453, 1946.

103. Lichtenstein, L., and Fox, L. J.: Necrotizing Arterial Lesions Resembling Those of Periarteritis Nodosa and Focal Visceral Necrosis Following Administration of Sulfathiazole: Report of a Case, Am. J. Path. **22**:665, 1946.

104. Werne, J., and Garrow, I.: Fatal Anaphylactic Shock: Occurrence in Identical Twins Following Second Injection of Diphtheria Toxoid and Pertussis Antigen, J. A. M. A. **131**:730 (June 29) 1946.

105. Wright, D. O., and Gold, E. M.: Löffler's Syndrome Associated with Creeping Eruption (Cutaneous Helminthiasis): Report of Twenty-Six Cases, Arch. Int. Med. **78**:303 (Sept.) 1946.

106. Blanton, H. W.: Observations on Löeffler's Syndrome-Report of Four Cases, Virginia M. Monthly **72**:473, 1945.

107. Henderson, A. T., and Pierre, C. B.: Transitory Focal Pulmonary Edema and Eosinophilia: Löeffler's Syndrome, Am. J. Roentgenol. **58**:391, 1947.

and Kinsey[108] injected horse serum into the trachea of sensitized rabbits and produced dyspnea comparable with asthma. Roentgenograms of the lungs showed transitory pulmonary infiltration in these rabbits. So far the pathologic changes of Loeffler's syndrome are not clear, for the condition is mild and patients do not die from it. Usually the appearance in the roentgenogram is accompanied with a high percentage of eosinophils in the blood smear.

A recent paper by Gregory and Rich[109] throws light on Loeffler's syndrome. Rabbits were given repeated intravenous injections of foreign protein, and, when some of them died in acute anaphylactic shock, study of the lungs showed small focal lesions with damage of the capillary wall, thrombosis and edema. In other animals which survived the treatment and were killed later, similar lesions were seen; they were comparable to the type of local lesions seen in the lung in rheumatic fever. Longcope[110] inoculated animals in 1914; dogs, cats and guinea pigs were sensitized to egg white alone, to horse serum alone or sometimes to both at the same time. After reinjection, focal infiltrations of the heart and kidneys were plainly visible. The observations should have led to a much longer series of experiments, for they were basically the same as those which Rich describes.

In tropical eosinophilia (called Weingarten's syndrome), asthma appears to be a fairly common symptom. However, the asthma and the syndrome itself can be cured rather easily with a few injections of arsenic compound, like neoarsphenamine, or sometimes simply with carbarsone pills given by mouth. The 2 patients whom Irwin[111] describes were treated with carbarsone and recovered completely. Another case is reported by Hunter[112]—asthma developed in a young man who had spent twelve years in Nigeria in about six months after he had returned to England. His blood smear showed up to 74 per cent of eosinophils. Three injections of an organic arsenic preparation cured him.

Loeffler's syndrome and tropical eosinophila are much alike. Arsenic compound cures the latter. Will it also cure Loeffler's syndrome? Is cure by arsenic compound a differential point? The question is not yet answered, presumably because the disease occurs rarely or, at least, it is not recognized, in this country.

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108. Herbut, P. A., and Kinsey, F. R.: Transitory Pulmonary Infiltrations (Löeffler's Syndrome) in Rabbits, Arch. Path. **41**:489 (May) 1946.

109. Gregory, J. E., and Rich, A. R.: Experimental Production of Anaphylactic Pulmonary Lesions with the Basic Characteristics of Rheumatic Pneumonitis, Bull. Johns Hopkins Hosp. **78**:1, 1946.

110. Longcope, W. T.: Effect of Repeated Injections of Foreign Protein on the Heart Muscle, Arch. Int. Med. **15**:1079 (June) 1915.

111. Irwin, J. W.: Tropical Eosinophilia, Ann. Int. Med. **25**:329, 1946.

112. Hunter, E. A.: A Case of Tropical Eosinophilia (Weingarten's Syndrome), Brit. M. J. **1**:877, 1946.

DIAGNOSIS OF ASTHMA

In an army general hospital, Rosen[113] studied 100 consecutive cases of asthma. He observed nasal symptoms in 45 and observed that they came before the asthma in about half the cases. Positive reactions to cutaneous tests occurred more frequently in the group of patients with nasal symptoms. Unger and his co-workers[114] classified the disease in their 97 cases into paroxysmal and chronic types. In all, 21.1 per cent of the patients were "cured," and, as expected, the better results were in the paroxysmal series. Waldbott[115] asks, "Is there an intrinsic asthma?" He selected 323 patients as having continuous symptoms. Positive reactions to cutaneous tests were seen in as many as 77 per cent, but the significance of these is not discussed. He recognizes that intrinsic causes—sensitivity to cold temperature, to endocrine products and to bacterial infections—"were definitely responsible for attacks in a large number. . . . Psychogenic factors, products of digestion or such physiological fluids as insulin, liver extract, colostrum may or may not play a part. In no case were such intrinsic factors found to be the only causes. . . ." Only 9 per cent of his patients were "cured." This type of disease is always difficult to deal with, since the cause is rarely simple or single, but it is my opinion that intrinsic factors, notably depletion, or stress and strain of various kinds, represent the important point. Waldbott has been frank enough to include an addendum to one report of a case: ". . . after being placed on a high caloric diet disregarding all positive foods, this patient has been practically free from asthma."

The chemical factors in asthma have been reviewed by Wiswell and Rackemann[116] in a study of the literature. It was observed that, so far at least, there is no evidence that disturbances of sodium, potassium or calcium or other metabolic factors play any constant role.

There are two interesting papers on bullous emphysema. Price and Teplick[117] describe 8 cases in which areas in one or other lobe, mostly in the apexes, is replaced by a cystlike area. Autopsy in 1 case showed two large sacs, with extremely thin walls, in which the air was under

113. Rosen, F. L.: Bronchial Asthma in the Young Male Adult: A Study of One Hundred Hospitalized Patients in an Army General Hospital, with Special Reference to Nasal Symptoms and Findings, Ann. Allergy **4**:247, 1946.

114. Unger, L.; Levy, H. A., and Eisele, I. B.: Outline on Bronchial Asthma, Scientific Exhibit, American Medical Association, Atlantic City, N. J., June 9-13, 1947.

115. Waldbott, G. L.: Is There an Intrinsic Asthma? Ann. Int. Med. **26**:863, 1947.

116. Wiswell, J. G., and Rackemann, F. M.: Chemical Factors in Asthma, New England J. Med. **237**:364 and 400, 1947.

117. Price, A. H., and Teplick, G.: Progressive Bilateral Bullous Emphysema, Arch. Int. Med. **77**:132 (Feb.) 1946.

pressure. All of their patients were men, and in all but 1 symptoms developed after the age of 45. Amberson and Spain[118] found the cause in their patient. A Negro, aged 44, had had wheezy colds, with persistent asthma later and then pneumonia. Autopsy showed that around many of the smaller bronchi there was a submucous organizing inflammation which encircled the airway to act as a check valve. During expiration, deflation of the bullae was much retarded. It is suggested that emphysema in later years may be referable to the proliferative changes with fibrosis around the bronchi which have followed early infectious processes.

TREATMENT OF ASTHMA

Drugs.—Epinephrine: Drugs are essential for the acute asthmatic attack. The recent literature says little about epinephrine, except that clinical reports here and there indicate that physicians have learned to use only small doses. For subcutaneous injection, a quantity as small as 0.25cc. of the 1 to 1,000 solution is often as effective, if not more so, than the large dose of 1 cc., which results in disagreeable side effects.

Aminophylline: Next to epinephrine in usefulness comes aminophylline for the relief of acute paroxysms. The usual dose is 0.25 Gm. dissolved in 10 cc. of isotonic sodium chloride solution and injected into the vein. Goodall and Unger[119] recommend the continuous injection of aminophylline, 2 or 3 Gm. in 2,000 cc. of 5 per cent dextrose solution in water. As much as 3.0 Gm. can be injected in this way in twenty-four hours without danger. Prigal, Fuchs and Schulman[120] report that suppositories containing 0.50 Gm. each were helpful to 25 out of 45 patients but that when 0.10 Gm. of pentobarbital sodium was added to the same amount of aminophylline in suppository form the mixture relieved 44 out of 47 patients. Evidently there is good reason for adding small doses of phenobarbital to the numerous pills and capsules now on the market, most of which contain ephedrine (25 mg.), aminophylline (250 mg.) and phenobarbital (10 mg.). Prigal, Brooks and Harris[121] describe the inhalation of aminophylline by means of an aerosol in steam. The steam passes into the nebulizer to carry with it small amounts of the solution of aminophylline contained therein.

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118. Amberson, J. B., and Spain, D. M.: A Mechanism Explaining Chronic Progressive Pulmonary Bullous Emphysema, Tr. A. Am. Physicians **60**:92, 1947.

119. Goodall, R. J., and Unger, L.: Continuous Intravenous Aminophyllin Therapy in Status Asthmaticus, Ann. Allergy **5**:196, 1947.

120. Prigal, S. J.; Fuchs, A. M., and Schulman, P. M.: Treatment of Asthma with Rectal Suppositories of Aminophylline and Sodium Pentobarbital, J. Allergy **17**:119, 1946.

121. Prigal, S. J.; Brooks, A. M., and Harris, R.: Treatment of Asthma by Inhalation of Aerosol of Aminophylline, J. Allergy **18**:16, 1947.

Alcohol: Brown[122] suggests that alcohol can be injected safely as a 5 per cent solution in isotonic solution of sodium chloride, together with 5 per cent solution of dextrose. Five out of 6 of his patients with severe asthma were relieved with this treatment.

Procaine Hydrochloride: The administration of procaine hydrochloride intravenously is a new idea. In 1946 State and Wagensteen[123] observed that as much as 1.0 Gm. of procaine hydrochloride dissolved in 500 cc. of isotonic sodium chloride solution could be injected intravenously without harm. When given to 16 patients with serum sickness, it effected immediate and complete relief from itching in 10. In a few cases, the dose had to be given a second time. Of 7 patients with urticaria, 6 were benefited by treatment with procaine hydrochloride. Durieu and his co-workers,[124] in Brussels, treated 25 patients with asthma with daily intravenous injections of from 5 to 20 cc. of 1 per cent solution of procaine hydrochloride. Lasting improvement was obtained in half the cases and temporary improvement in another 30 per cent. When, however, the asthma was complicated by emphysema and severe bronchitis, only 30 per cent of the patients showed any improvement, and this was only temporary. Appelbaum, Abraham and Sinton[125] describe a boy of 16 with serum disease following the administration of tetanus antitoxin who was relieved within two hours following an intravenous injection of 1 Gm. of procaine hydrochloride in 500 cc. of isotonic solution of sodium chloride. Dressler and Dwork[126] describe a woman of 42 who had had a thoracoplasty for tuberculosis and was treated with large doses of penicillin. In the meantime, 3 Gm. of sulfathiazole crystals had been dusted into her wound after each of the two stages of operation. On the night of the second stage, giant urticaria appeared, and for three days she had a fever, a rash and joint pains. All this, however, was relieved within ten minutes after a slow drip of isotonic solution of sodium chloride (500 cc.) containing 1 Gm. of procaine hydrochloride was started in her vein.

Ephedrine is always useful. Herxheimer[127] does well to point out that whereas small doses, up to 50 mg., may do neither good nor harm,

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122. Brown, E. A.: The Use of Intravenous Ethyl Alcohol in the Treatment of Status Asthmaticus, Ann. Allergy **5**:193, 1947.

123. State, D., and Wangensteen, O. H.: Procaine Intravenously in Treatment of Delayed Serum Sickness, J. A. M. A. **130**:990 (April 13) 1946.

124. Durieu, H.; De Clercq, F., and Duprez, A.: Treatment of Asthma with Intravenous Administration of Procaine Hydrochloride, Acta clin. belg. **1**:150, 1946.

125. Appelbaum, E.; Abraham, A., and Sinton, W.: A Case of Serum Sickness Treated with Procaine Intravenously, J. A. M. A. **131**:1274 (Aug. 17) 1946.

126. Dressler, S., and Dwork, R. E.: Reactions to Penicillin: Procaine Hydrochloride Intravenously in the Treatment of Reactions Similar to Serum Sickness, J. A. M. A. **133**:849 (March 22) 1947.

127. Herxheimer, H.: Dosage of Ephedrine in Asthma and Emphysema, Brit. M. J. **1**:343, 1946.

there are patients who will be benefited if the dose is increased to 100 or even 200 mg., given three or four times a day. He warns, however, that a tolerance to ephedrine is acquired rather quickly, so that intermittent treatment, for not more than three days at a time, followed by two or three days without the drug, is often a satisfactory method of treatment for severe intractable asthma.

Basic Treatment.—The concern in the basic treatment of asthma is first of all with the patient as a whole; he needs confidence and reassurance as part of nursing care. The subject was discussed by Rackemann,[128] in 1942, in a paper on the treatment of the asthmatic attack, and now a paper by Carryer and his co-workers[129] from the Mayo Clinic describes a similar point of view. The psychosomatic factors in asthma as part of depletion were discussed in an earlier section. They are always important—so much so that I believe that many of the active types of treatment do good because they provide tangible evidence that something can be done. The treatment of the patient is usually more important than the treatment of his asthma.

Nonspecific Treatment: Nonspecific treatment is of various kinds. Cohen and Friedman[130] have used a total of 3 liters of histamine azoprotein ("hapamine") and record their experiences. In 15 cases of urticaria, the results were excellent in 8 and good in 3. In 19 cases of asthma, results were excellent in 8 and good in 1. In other conditions, however, the results were not so good. Dundy, Zohn, and Chobot[131] report on 40 patients, 20 of whom were children. Their results with histamine azoprotein were disappointing. Whereas the drug is supposed to build up a tolerance to histamine, they observed that the reaction to a cutaneous test with histamine, made after the treatment, was the same as that elicited before the treatment was begun.

Godlowski[132] has used insulin shock, giving 20 units of insulin two to three times a week and controlling the severity by feeding dextrose. Eight patients with allergic asthma were treated, and 7 responded with complete recovery, which lasted two and a half years in 1 patient. I wonder what changes in the environment were made at the same time and emphasize again that the results of any treatment in true allergic asthma must be appraised cautiously. In 3 other patients with nonallergic asthma, Godlowski observed no results with inuslin shock.

128. Rackemann, F. M.: The Treatment of the Asthmatic Attack, M. Clin. North America **26**:1501, 1942.

129. Carryer, H. M.; Prickman, L. E.; Maytum, C. K., and Koelsche, G. A.: Treatment of Seriously Ill Asthmatic Patient, J. A. M. A. **131**:21 (May 4) 1946.

130. Cohen, M. B., and Friedman, H. J.: Histamine Azoprotein in the Treatment of Allergy, J. Allergy **18**:7, 1947.

131. Dundy, H. D.; Zohn, B., and Chobot, R.: Histamine Azoprotein: Chemical Evaluation, J. Allergy **18**:1, 1947.

132. Godlowski, Z.: Insulin Shock Treatment of Bronchial Asthma, Brit. M. J. **1**:717, 1946.

Mechanical Procedures.—Mechanical procedures have been devised. At the Johns Hopkins Hospital, Crowe[133] became interested in the treatment for deafness by the removal of the lymphoid tissues in the nasal pharynx by means of radium. At his suggestion the method was tried by Gay[134] in patients with asthma and was found useful, and Ward, Livingston and Moffat[135] report the results in 34 children with asthmatic bronchitis. The lymphoid tissue disappeared in 23 of these 34 children, and, as a result, 15 children were relieved completely of their asthma and 5 others had only occasional mild attacks. The results were good, but they were not perfect, and again I wonder about controls. It is my experience that asthma in children is not too difficult to deal with, since allergy to dusts of various kinds is so often responsible.

Bronchoscopy: Bronchoscopy for diagnosis is sometimes useful, particularly when the roentgenogram gives evidence of local areas of collapse. When these areas are located fairly close to the hilus region, bronchoscopy may reveal the cause of the bronchial obstruction and so lead to appropriate treatment. Bronchoscopy for treatment *per se* has been tried, the idea being to remove the tough sticky plugs which occlude the bronchi. The procedure is drastic, and I have seen a patient, a healthy woman in her forties, whose asthma was severe, die on the table with the bronchoscope in place. The preliminary apprehension and the exertion of the procedure increased the difficulty with respiration, until it was more than she could tolerate.

In a recent paper Lell[136] describes the bronchoscopic study of 176 children with asthma. Foreign bodies in the bronchi were seen in 18 and in the esophagus in 5. Other lesions were observed in 23 others. The bronchial mucosa was edematous and engorged, and most of the patients showed a narrowing of the bronchial lumen. In some cases the removal of the pulmonary secretion was life saving.

Penicillin.—As soon as penicillin became generally available, in 1944, it was used for asthma. Cooke[87] was one of the first to observe its good effects, and he described several patients with chronic infections of the sinuses and bronchi who were relieved by penicillin injections. Soon after this, Barach[137] began using penicillin in the form of a mist or vapor,

133. Crowe, S. J.: Local Use of Sulfadiazine Solution, Radon, Tyrothricin and Penicillin in Otolaryngology, Ann. Otol., Rhin. & Laryng. **53**:227, 1944.

134. Gay, L. N.: Treatment of Residual Lymphoid Tissue in Nasopharynx by Radium, J. Allergy **17**:348, 1946.

135. Ward, A. T., Jr.; Livingston, S., and Moffat, D. A.: Asthma in Children: Treatment with the Radium Nasopharyngeal Applicator, J. A. M. A. **133**:1060 (April 12) 1947.

136. Lell, W. A.; Bronchoscopy as Aid in Diagnosis and Treatment of Allergic Pulmonary Disease, Arch. Otolaryng. **43**:49 (Jan.) 1946.

137. Barach, A. L.: Penicillin Aerosol and Negative Pressure in the Treatment of Sinusitis, Am. J. Med. **1**:268, 1946.

which could be inhaled. Since then, penicillin, given by injection or in the form of an aerosol, has been used by numerous workers in pulmonary disease of every kind, and on the whole the results have been good. In a comprehensive article written in 1945, Vermilye[138] reviewed the literature; he described the technic by which a small amount of concentrated penicillin solution (50,000 units per cubic centimeter) was placed in a "vaponephrin" nebulizer, so arranged that a pressure of oxygen would flow through the nebulizer whenever the patient put his finger on the end of the open Y on the tube connection. It is important that the patient learn to correlate the flow of penicillin vapor with his own inspiration. In all sorts of acute and chronic infections of the bronchi and lungs, penicillin aerosol has been tried and observed to be effective in a large proportion of the cases. Segal and Ryder[139] in Boston have used much the same apparatus. In pneumonia the results are good; in bronchiectasis and pulmonary abscess the patients are benefited, but not cured. In "infective bronchial asthma" the treatment was given to 22 patients in courses lasting from three days to three weeks. No figures are given in the latest paper, but a sentence reads: "This therapy was generally disappointing, although striking improvement was occasionally observed." In the 6 cases of pulmonary emphysema the results were excellent. Segal used 1 cc. of a solution containing 25,000 units of calicum or sodium penicillin, which is placed in the "vaponephrin" atomizer and blown through with oxygen pressure. Blood levels ranging from 0.15 up to 0.225 units per cubic centimeter were obtained, but, as expected, these levels fell to 0 within two hours. Treatment with penicillin must be repeated frequently.

In his paper, Barach[137] has summarized his results with treatment of sinusitis with penicillin aerosol. A total of one hundred and twenty-two courses of treatment was given to 110 patients—some with acute and most with chronic sinusitis—and the protocol indicates that at least half of them had asthma. Unfortunately, the ages of these patients are not given, nor is there any statement concerning the kind of asthma which they had. One would like to assume that most of these patients were older persons, with the kind of asthma which is of intrinsic origin and associated with polypoid sinusitis. With one hundred and twenty-two courses, decided improvement was obtained in 39 cases—about 30 per cent—and moderate improvement was obstained in another 43 cases, or 35 per cent, on the whole a good showing. In the "good" group, roentgenograms of the sinuses taken before and after treatment showed virtual clearing in about half the cases, and cultures taken before and

138. Vermilye, H. N.: Aerosol Penicillin in General Practice, J. A. M. A. **129**:250 (Sept. 22) 1945.

139. Segal, M. S., and Ryder, C. M.: Penicillin Inhalation Therapy, New England J. Med. **236**:132, 1947.

after treatment showed a striking change. In 24 of 41 cases in which cultures were made, all gram-positive organisms were cleared entirely with the penicillin aerosol, leaving behind the gram-negative organism. Southwell,[140] in England, had a smaller series of patients—43 in all—but they included 17 with "chronic bronchitic asthma." Of these, I was cured and 13 were improved with the penicillin inhalations. Four patients with asthma were treated, but without results. Whereas the technic involving a fancy nebulizer and an oxygen tank is rather difficult, Morse,[141] a "country doctor" in Nova Scotia, has pointed out that a simple penicillin spray can be obtained easily with a "DeVilbiss no. 15" atomizer, activated by a hand bulb. He dissolves 100,000 units of penicillin in 10 cc. of sterile water and places the whole solution in the atomizer chamber. The patient is instructed to squeeze the bulb during every inspiration for ten minutes every hour and then after four treatments to repeat for ten minutes once every four hours while awake. This simple method was used by Dr. Morse for the treatment of all sorts of pulmonary disease, and he obtained good results with it. Fincke[142] also has a simple method; he suggests that a bicycle pump gives abundant air under sufficient pressure and with little effort, and if the pump is in good condition the spray can be activated through several inspirations with only one down stroke.

In the meantime, penicillin given by injection, as used originally by Cooke, may still be important. Leopold[143] advised that 40,000 units be injected at intervals of four hours, to total 240,000 units a day. He used the method in 85 cases of asthma, in 62 of which the disease was of the perennial intrinsic type and 20 of the allergic type. Unfortunately, the results were not good. The wheeze was decreased in 26 patients, or 41 per cent, but only 10 patients, or 16 per cent, enjoyed any continued improvement. For secondary infections in asthma, as in many other conditions, penicillin is useful, but the fact that penicillin does not always produce striking benefit in patients with asthma is in itself some argument that an infection is not the primary cause of trouble. It is my opinion that treatment with penicillin in all forms should be reserved for those cases in which the evidence of active infection is good.

Reactions to Penicillin.—Reactions to penicillin do occur, the commonest being urticaria, of the serum sickness type, which, like the reaction to serum itself, develops after an interval of several days and runs a

140. Southwell, N.: Inhaled Penicillin in Bronchial Infections, Lancet **2**:225, 1946.

141. Morse, F. W.: Penicillin Spray by Bulb Atomizer in Respiratory Infections, J. A. M. A. **132**:272 (Oct. 5) 1946.

142. Fincke, W.: Simplification of Penicillin Aerosol Therapy for Home Treatment, Am. Pract. **1**:643, 1947.

143. Leopold, H. C.: Penicillin Therapy in Chronic Bronchial Asthma, J. Allergy **17**:166, 1946.

rather similar course. Figures for the incidence are quoted by Gordon[144] as follows: Keefer observed urticarial reactions in 14 of 500 patients, or 2.9 per cent. Lyons observed them in 12 out of 209 patients, or 5.7 per cent, Moore in 8 out of 1,418, or 0.56 per cent, and Stokes in only 2 out of 192 patients (1.2 per cent). Romansky[145] reports allergic reactions, mostly urticaria and angioneurotic edema, in 5 per cent of 600 patients treated with intramuscular injections of calcium penicillin in wax and peanut oil. Most of them occurred on the fourth day.

How can one tell whether a given patient is sensitive or not—whether a reaction will occur? Callaway and Barefoot[146] made studies in 5 patients who had experienced urticaria following penicillin therapy. Cutaneous tests were made by the intracutaneous and passive transfer methods, and precipitin tests were made, but none of these laboratory procedures gave positive results. In a general article on allergy to drugs, Sherman[147] declares that the reaction neither to cutaneous tests nor to passive transwer with the Prausnitz-Kustner technic is a reliable index of penicillin sensitivity. On the other hand, Peck and Siegal[148] observed a positive reaction to a cutaneous test in a man of 63 in whom a diffuse eruption developed after parenteral administration of penicillin, and when the lesions subsided the second dose of penicillin elicited the reaction once more. After that small doses of penicillin were given at frequent intervals and desensitization was finally accomplished, so that the effective dosage, which the man needed, could be given.

As in other allergies to drugs, the best method of prevention of reaction is in the physician's thinking of allergy and then asking two questions: First: "Have you ever had hay fever, asthma or peculiar reactions?" That is to say: "Is this patient an allergic person with the asthmatic state? Second, "Have you ever been given this drug before, and if so did the dose disturb you in any way?" In other words: Has this patient been sensitized?

Local sensitiveness to penicillin may develop when it is used locally in sprays, nose drops or ointments. Hopkins and Lawrence[149] observed that penicillin ointment produced local sensitiveness of the skin, as de-

144. Gordon, E. J.: Delayed Serum Sickness Reaction to Penicillin, J. A. M. A. **131**:727 (June 29) 1946.

145. Romansky, M. J.: The Current Status of Calcium Penicillin in Beeswax and Peanut Oil, Am. J. Med. **1**:395, 1946.

146. Callaway, J. L., and Barefoot, S. W.: Immunological Studies on Patients Developing Urticaria Associated with Penicillin Therapy, J. Invest. Dermat. **7**:285, 1946.

147. Sherman, W. B.: Drug Allergy, Am. J. Med. **3**:586, 1947.

148. Peck, S. M., and Siegal, S.: Successful Desensitization in Penicillin Sensitivity, J. A. M. A. **134**:1546 (Aug. 30) 1947.

149. Hopkins, J. G., and Lawrence, H.: Sensitization to Penicillin, J. Allergy **18**:251, 1947.

termined by positive reactions to patch tests, in 13 per cent of the patients treated. Goldman and Mason[150] treated 350 patients with penicillin ointment and observed that reactions to patch tests were positive in 134, or 38 per cent. In 1 of the patients there developed generalized exfoliative dermatitis. Cormia and his co-workers[151] have shown that in animals penicillin shows all the characteristics of a good allergenic substance. Single doses of commercial penicillin sensitize guinea pigs, so that the uterus reacts well in the Dale bath.

ALLERGY TO DRUGS IN GENERAL

There are two papers which deal with allergy to drugs in its broad aspects. Sherman's[147] paper has been noted. He describes the symptoms, the mechanism and the methods of diagnosis in detail.

In his article, Dragstedt[152] points out that certain "idiosyncrasies" may not be allergic: the mechanism may depend on other factors. In rats, for example, sulfathiazole inhibits folic acid and so leads to granulocytopenia. Reactions to neoarsphenamine can be reduced or prevented by treatment with ascorbic acid, which inhibits the oxidation of the drug and so prevents the formation of toxic breakdown products. The polyneuritis, which results sometimes from treatment with sulfonamide drugs, may depend on a deficiency of vitamin B_1, which predisposes the tissue to injury by drugs. Dragstedt sets up provisional criteria for the diagnosis of allergy to drugs as follows:

1. The reaction pattern must be consistent with allergic manifestations; it must include urticaria, asthma, rhinitis or dermatitis.
2. There should be a history of a primary or sensitizing dose followed by an interval, and the reaction should follow promptly when the new treatment is given.
3. Treatment with epinephrine and other sympathetic stimulants should relieve the symptoms, as they do in more typical allergy.

Sulfonamide Drugs.—The sulfonamide drugs are important sensitizers, and the cause of many allergic reactions due to drugs. Local treatment with the sulfonamide drugs, in the form of wet dressings or ointments, appears to be particularly important. Sulzberger and his coworkers[153] experimentally produced small burns, about 1 cm. in diameter,

150. Goldman, L.; Friend, F., and Mason, L.: Dermatitis from Penicillin, J. A. M. A. **131**:883 (July 13) 1946.

151. Cormia, F. E.; Lewis, B. M., and Hoppe, M. E.: Experimental Aspects of Penicillin Sensitization: II. With Reference to the Schultz-Dale Phenomenon, J. Invest. Dermat. **8**:395, 1947.

152. Dragstedt, C. A.: Idiosyncrasy to Drugs, J. A. M. A. **135**:133 (Sept. 20) 1947.

153. Sulzberger, M. B.; Kanof, A.; Baer, R. L., and Lowenberg, C.: Sensitization by Topical Application of Sulfonamides, J. Allergy **18**:92, 1947.

in the skin of normal persons and then treated these burns with various sulfonamide preparations. In all, 264 men were subjected to the experiment. Of these, 49 were treated with a 5 per cent sulfadiazine cream, and of this number, 57 per cent experienced localized dermatitis on the treated spot. With other sulfonamide creams the incidence was much smaller, and the authors demonstrated that the sensitizing potentials corresponded rather accurately to the degree of solubility of the drug in water. Two factors were important. The skin must be damaged before the ointment is applied, and previous exposure to the drug materially increased the number and severity of reactions obtained.

Dowling, Hirsh and Lepper[154] observed that the patient who had previously experienced fever, dermatitis or conjunctivitis from a reaction to drugs was likelier than some other person to experience a similar reaction during subsequent treatment. Among 48 patients to whom the same sulfonamide drug was given another time, 33, or 69 per cent, experienced toxic reactions, but, among 30 other patients who received a different sulfonamide drug, only 5, or 17 per cent, reacted. Sherman and Cooke[155] observed positive reactions to cutaneous and passive transfer tests in a woman sensitive to sulfadiazine, but no such reaction in 2 other patients.

Influenza Vaccine.—Reactions to influenza, yellow fever and perhaps to typhus vaccine are being noted with the increasing use of these preparations. Stull[156] has observed that the chick embryo yolk sac vaccines do contain sufficient egg protein to cause severe systemic reactions if given to persons sensitive to eggs. Ratner and Untracht,[157] on the other hand, observed that whereas 10.2 per cent of 108 allergic children were sensitive to egg, only 4.6 per cent were sufficiently sensitive to make the treatment dangerous. The paper contains a full discussion. Curphey[158] describes the fatal reaction which followed an injection of influenza A and B vaccine in a young girl aged 3½ years. Four hours later the child had pain in her stomach, chills, vomiting and a temperature of 109 F.

154. Dowling, H. F.; Hirsh, H. L., and Lepper, M. H.: Toxic Reactions Accompanying Second Courses of Sulfonamides in Patients Developing Toxic Reactions During a Previous Course, Ann. Int. Med. **24**:629, 1946.

155. Sherman, W. B., and Cooke, R. A.: Sulfadiazine Sensitivity with Demonstrable Skin-Sensitizing Antibody in the Serum, Am. J. Med. **11**:588, 1947.

156. Stull, A.: Allergenic and Anaphylactogenic Properties of Vaccines Prepared from Embryonic Tissues of Developing Chicks: III. A Study to Determine Whether Chick-Embryo Yolk-Sac Vaccines Contain Sufficient Egg Proteins to Cause Severe Systemic Reactions if Given to Egg-Sensitive Individuals, J. Immunol. **53**:343, 1946.

157. Ratner, B., and Untracht, S.: Allergy to Virus and Rickettsial Vaccines: I. Allergy to Influenza A and B Vaccine in Children, J. A. M. A. **132**:899 (Dec. 14) 1946.

158. Curphey, T. J.: Fatal Allergic Reaction Due to Influenza Vaccine, J. A. M. A. **133**:1062 (April 12) 1947.

(by rectum). In the hospital cyanosis and convulsions developed, and she died in seven hours, despite treatment with oxygen, epinephrine and bleeding. The autopsy did not reveal that death was due to anaphylaxis. The lungs showed an early pneumonic reaction, which was comparable, perhaps, to the Schwartzman phenomenon. Rifkin[159] reports the death of a man aged 24 about twenty-five minutes after the injection of 1 cc. of typhus vaccine. In his case there was a history of previous sensitiveness to egg, and autopsy showed the characteristic emphysema of anaphylaxis. Rubin[160] reports a soldier who had hay fever and had been sensitive to eggs all his life. After a dose of yellow fever vaccine, prepared from infected chick embryos and typhus vaccine prepared from infected yolk sacs, angioneurotic edema and asthma developed.

Iodopyracet ("Diodrast").—Allergic reactions to drugs may result from preparations used in diagnosis as well as in treatment. Reactions to iodopyracet injection ("diodrast"), used for roentgenograms of the kidney, are not uncommon. Alyea and Haines[161] present some interesting figures concerned with the use of iodopyracet in 1,675 cases. Reactions to cutaneous tests made on all of these were positive in 15 per cent. Of the subjects with positive cutaneous reactions, only 16 per cent showed any systemic reaction when the drug was injected. Moreover, in the subjects with negative reactions to the cutaneous test, systemic reactions occurred in 4 per cent. Discrepancies occurred in both directions. When the patient was also allergic, reactions to cutaneous tests with iodopyracet occurred in a larger percentage. As expected, these patients showed their capacity for development of sensitiveness to foreign substances. More recently I have heard that a better test for sensitivity to iodopyracet consists in injecting intravenously 1.0 cc. of a 1 to 20 dilution of the material which is to be used undiluted later. If the patient is sensitive, the small dose will produce a reaction and give the warning.

Congo Red.—Congo red used for the study of amyloid disease can cause systemic reaction after intravenous administration. Selikoff and Bernstein[162] observed 100 consecutive cases, with severe systemic reactions in 6 cases and death in 2.

Iodized Oil.—Iodized oil used in bronchoscopy is another offender.

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159. Rifkin, H.: Death Due to Administration of Typhus Vaccine, Ann. Int. Med. **25**:346, 1946.

160. Rubin, S. S.: Allergic Reaction Following Typhus Fever Vaccine and Yellow Fever Vaccine Due to Egg Yolk Sensitivity, J. Allergy **17**:21, 1946.

161. Alyea, E. P., and Haines, C. E.: Intradermal Test for Sensitivity to Iodopyracet Injection, or "Diodrast," J. A. M. A. **135**:25 (Sept. 6) 1947.

162. Selikoff, I. J., and Bernstein, I. J.: Systemic Reactions to the Intravenous Administration of Congo Red, Quart. Bull., Sea View Hosp. **8**:131, 1946.

Mahon[163] found 10 cases in the literature and adds the report of a man who received 10 cc. of "lipiodol" (iodized poppy seed oil 40 per cent) in each lung; twenty minutes later convulsions developed, and he died. His tracheobroncial tree was observed to be completely filled with sticky mucus.

Drugs Used for Treatment.—These drugs are often more important. Thiouracil may produce granulocytopenia. Morton[164] reviewed 59 cases reported in the literature and added 2 more. Reingold and Webb[165] treated a young woman with intravenous injections of thiamine hydrochloride. The first dose of 100 mg. caused an immediate burning sensation and sweating, but it passed. Three days and twenty days later, respectively, the second and third doses produced no symptoms, but the fourth dose, given on the thirty-fifth day, caused immediate dyspnea, with cyanosis and death. Nicotinic acid ("niacine") is injected occasionally for severe vitamin deficiency or because of its vasodilating action. Pelner[166] reports 2 patients who suffered severe systemic disturbances after relatively small doses. Livingston and Livingston[167] report another case of granulocytopenia and jaundice after treatment with propylthiouracil (a thiourea derivative). Agress[168] reports reactions to quinacrine hydrochloride ("atabrine")—5 cases among Chinese soldiers, which represents one reaction in every 2,000 or 3,000 cases. Each soldier experienced severe exfoliative dermatitis and hepatitis, beginning on the second or sometimes the tenth day. Four of the 5 soldiers gave positive reactions to patch tests with quinacrine hydrochloride; all had eosinophilia, and 3 of the 5 died. Wright, Doan and Haynie[169] describe a student of 22 who sprayed his room with an aerosol bomb containing dichlorodiphenyltrichloroethane (D D T). Ten days later sore throat developed, and he was observed to have a white cell count of only 3,800 with only 1 polymorphonuclear cell in the smear. Fortunately,

163. Mahon, G. S.: Reaction Following Bronchography with Iodized Oil, J. A. M. A. **130**:194 (Jan. 26) 1946.

164. Morton, J. H.: Agranulocytosis Caused by Thiouracil: A Review of Fifty-Nine Cases in the Literature and a Report of Two Additional Cases, Am. J. Med. **2**:53, 1947.

165. Reingold, I. M., and Webb, F. R.: Sudden Death Following Intravenous Injection of Thiamine Hydrochloride, J. A. M. A. **130**:491 (Feb. 23) 1946.

166. Pelner, L.: Anaphylaxis to the Injection of Nicotinic Acid (Niacin): Successful Treatment with Epinephrine, Ann. Int. Med. **46**:290, 1947.

167. Livingston, H. J., and Livingston, S. F.: Agranulocytosis and Hepatocellular Jaundice: Toxic Reactions Following Propylthiouracil Therapy, J. A. M. A. **135**:422 (Oct. 18) 1947.

168. Agress, C. M.: Atabrine as a Cause of Fatal Exfoliative Dermatitis and Hepatitis, J. A. M. A. **131**:14 (May 4) 1946.

169. Wright, C. S.; Doan, C. A., and Haynie, H. C.: Agranulocytosis Occurring After Exposure to a D.D.T. Pyrethrum Aerosol Bomb, Am. J. Med. **1**:562, 1946.

the prompt injection of penicillin prevented the development of an infection of the respiratory tract. It is extraordinary that foreign serum is still being used from time to time, and with little attention to its dangerous possibilities. From England comes the report of Gardner[170] describing the physician who was called to see a small boy who had crushed his hands. By telephone he ordered the immediate injection of 3,000 units of tetanus antitoxin. Almost at once the boy complained of feeling ill, and in an hour he was dead. No questions had been asked about previous administration of horse serum, and no thought had been given to the possibility of allergy.

Finally, Friedlaender and Feinberg[171] discussed the problem of allergy to acetylsalicylic acid—a clinical factor which is of considerable practical importance in certain patients with asthma. The allergy to acetylsalicylic acid denotes a severe type of asthma. The condition is typical of allergy to drugs. Cutaneous tests with acetylsalicylic acid elicit no reaction, and so far there is no way except that of clinical trial for recognizing the condition. Feinberg adds: "If aspirin sensitiveness can develop in this insidious manner, why cannot the patient be sensitive to any number of other substances non-protein in nature?" It is a troublesome thought.

Chase's Work on Drug Allergy.—The work done by Landsteiner has been continued by Chase. Chase[172] gives evidence that the sensitization of animals with simple chemical compounds is, in fact, mediated by an antibody mechanism which is comparable to that seen in more ordinary allergy. Chase inoculated guinea pigs intradermally with a series of doses of a chemical given four or five days apart over a period of five to twelve weeks. He observed that toward the end of treatment the serum of the animal was able to transfer the reaction capacity to the skin of a normal recipient guinea pig. When the cutaneous sites of these recipient animals were tested with the original chemical, reactions of the immediate urticarial type, often with pseudopods, were observed. These reactions were highly specific. Thus, if the sensitizing serum was obtained from an animal prepared by painting with picryl chloride, the reaction in the recipient animal could be elicited only with that drug; the recipient showed no reaction when the site was tested, for example, with orthochlorobenzylchloride. In another experiment Chase could demonstrate that the sensitive serum was active enough to produce typical passive anaphylaxis in a recipient animal. By this work, Chase has dem-

170. Gardner, E.: Rapid Death Following Injection of Antitetanic Serum. Lancet **1**:689, 1946.

171. Friedlaender, S., and Feinberg, S. M.: Aspirin Allergy: Its Relationship to Chronic Intractable Asthma, Ann. Int. Med. **26**:734, 1947.

172. Chase, M. W.: Studies on the Sensitization of Animals with Simple Chemical Compounds: X. Antibodies Inducing Immediate-Type Skin Reactions, J. Exper. Med. **86**:489, 1947.

onstrated that the antibodies involved in allergy to drugs, particularly in that type of allergy which has been called contact dermatitis, the antibodies are of the same type as those seen in typical anaphylaxis. The allergens used here are "poor" allergens. Nevertheless, when the experimental animals are treated long enough, antibodies develop and reactions occur the same as when other animals are treated with "good" allergens, like egg white or horse serum. As Chase points out, immediate urticarial wheal and erythema reactions to cutaneous tests are seen occasionally in patients with allergy to drugs. He notes Kern's patients sensitive to phthalic anhydride, Feinberg and Watson's patient sensitive to dichloramine T. and Sherman and Cooke's patients sensitive to sodium sulfadiazine; all these are authentic cases. Whereas such reactions are rare, the fact that they occur at all in the clinic confirms the principles which Chase has now demonstrated in the laboratory.

In another paper, Chase[173] has pointed to another mechanism which has a possible clinical bearing. When his experimental animals receiving treatment with a series of intradermal doses of a drug, like dinitrochlorobenzene, were fed by mouth a small quantity of the same chemical, the demonstration of sensitiveness did not occur. The treatment given beforehand had induced a state of resistance against subsequent experimental cutaneous sensitization by the same substance.

The whole concept of allergy to drugs is interesting, partly because of the difficulty in diagnosis, but more because the sensitiveness is directed to substances which are not proteins; they are simple chemical compounds. Occasionally the reactions to cutaneous tests are positive, but the discrepancies between the positive reactions to cutaneous tests and the subsequent systemic reactions are rather disconcerting. With respect to iodopyracet, even when the reaction to the cutaneous test is positive, the intravenous injection may proceed without difficulty, and then in other cases when the reaction is completely negative the subsequent injection causes trouble. The whole problem of allergy to drugs is of great practical importance, and it needs much further study.

HAY FEVER

The recent literature on hay fever has been reviewed by Kaplan,[174] and only a few points need be mentioned here. New pollen surveys appear from time to time; they are essential, for no physician can treat hay fever without understanding the pollens in his own environment.

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173. Chase, M. W.: Inhibition of Experimental Drug Allergy by Prior Feeding of the Sensitizing Agent, Proc. Soc. Exper. Biol. & Med. **61**:257, 1946.

174. Kaplan, M. A.: Progress in Allergy: Hay Fever; a Review of the Literature of 1946, Ann. Allergy **5**:253, 1947.

Clinical studies on hay fever are interesting. Brown and his coworkers[175] observed that 26 out of 38 pollen-sensitive persons showed a diminished vital capacity during the pollen season, even though they were free of asthma at the time the measurements were made. Rackemann[176] demonstrated that the level of pollen tolerance is of practical importance in the treatment of hay fever. The level at which systemic reactions can be produced by excessive treatment remains fairly constant for each patient. Doses just below this reaction level can be given without danger, and doses near that level will do good. The concept of an optimal zone of treatment dosage is confirmed. Alexander and Johnson[177] have compared the concentration of ragweed antibodies with circulating antigens and compared these two with the symptoms and the results of treatment. It is interesting to see pollen antigens and circulating pollen antibodies occurring together; one would expect them to precipitate each other out of solution. It is not clear why this does not happen. As for the results of treatment, they bear little relation to the laboratory observations.

Molds are more interesting than pollens, if only because the whole problem of molds is so complex. Bieberdorf and Hampton[178] made a twelve months' survey of air-borne molds in San Antonio, Texas. Hormodendron and Alternaria were commoner than other molds. Of 186 patients who reacted to tests with molds, all but 6 gave a history compatible with sensitiveness to molds. In contrast, Blumstein[179] observed that 41 of 101 patients reacted to one or more of thirteen mold extracts, but that only 12 of these 41 were clinically sensitive. Fraenkel[180] studied 522 patients with asthma in England and observed 84 who gave positive reactions to cutaneous tests with molds. Hyde and Williams[181] present graphs of the pollens and molds observed in the air over Eng-

175. Brown, E. A.; Nobili, C.; Sannella, T., and Wadsworth, G. P.: Dyspnoea and Diminished Vital Capacity as a Symptom and a Sign in Hay Fever, Dis. of Chest **12**:205, 1946.

176. Rackemann, F. M.: Pollen Tolerance: Its Bearing on the Treatment of Hay Fever, J. Allergy **18**:164, 1947.

177. Alexander, H. L.; Johnson, M. C., and Alexander, J. H.: Measurement of Circulating Ragweed Antibodies and Antigen: Correlation with Symptoms and Treatment, J. Allergy **17**:340, 1946.

178. Bieberdorf, F. W., and Hampton, S. F.: Airborne Fungi in Allergic Disease: II. Survey of Airborne Fungi in San Antonio, Texas, Area; Incidence of Skin Reactions with Mold Extracts, Ann. Allergy **4**:23, 1946.

179. Blumstein, G. I.: Mold Allergy: II. Clinical Analysis, Ann. Allergy **3**:341, 1945.

180. Fraenkel, E. M.: Bronchial Asthma and Mold Fungus Allergy, Schweiz. med. Wchnschr. **77**:115, 1947.

181. Hyde, H. A., and Williams, D. A.: A Daily Census of Alternaria Spores Caught from the Atmosphere at Cardiff in 1942 and 1943, Tr. Brit. Mycol. Soc. **29**:78, 1946. Studies in Atmospheric Pollen: I. A Daily Census of Pollens at Cardiff (Wales) 1942, New Phytologist **43**:49, 1944.

land. Alternaria is common; it reaches sharp peaks in August and September each year.

The difficulty with all these reports is that molds occur not only in many genera, but in hundreds of species within each genus. The problem of specificity among these species has been shown by the "Guba" experiment, in which Rackemann and his co-workers[182] demonstrated that 3 patients were sensitive specifically to one particular species in the Cladosporium genus. Cutaneous tests with related species using extracts prepared in precisely the same manner elicited essentially negative reactions. If this process of mold specificity is widespread, how shall one cope with it? Is it any wonder that the literature concerning allergy to molds is so difficult to deal with?

ECZEMA

The consideration that the kind of eczema which occurs in infancy and in young persons, which involves the face, neck and cubital and popliteal spaces and is called "flexural eczema," "neurodermite" or "atopic eczema," may be due to disturbances in fat metabolism is not new, but in recent years interest in it has been rearoused. In 1929 and 1930, Burr and Burr[183] published two papers on the effects of a rigid exclusion of all fat from the diet of rats. They observed that the unsaturated fatty acids, especially linolic and arachidonic acids, were essential for growth and reproduction in rats, but, more important, these elements were necessary for the nutrition and the integrity of the skin of the animals. Without these fatty acids the skin became dry and scaly and the hair became coarse and scanty.

In 1933, Hansen[184] observed that in certain patients with infantile eczema there were changes in the serum lipids, and he claimed that the feeding of fats was of benefit. In 1941, Finnerud and his assistants[185] took up the problem and confirmed the fact that the feeding of lard was useful in eczema. In the next year, Burr[186] wrote a comprehensive review of the subject, presenting the photographs of an infant with severe eczema before treatment and with clear skin after the administration of

182. Rackemann, F. M.; Randolph, T. G., and Guba, E. F.: The Specificity of Fungous Allergy, J. Allergy **9**:447, 1938.

183. Burr, G. O., and Burr, M. M.: A New Deficiency Disease Produced by Rigid Exclusion of Fats from Diet, J. Biol. Chem. **82**:345, 1929; On Nature and Role of Fatty Acids Essential to Nutrition, ibid **86**:587, 1930.

184. Hansen, A. E.: Serum Lipid Changes and Therapeutic Effects of Various Oils in Infantile Eczema, Proc. Soc. Exper. Biol. & Med. **31**:160, 1933.

185. Finnerud, C. W.; Kesler, R. L., and Wiese, H. F.: Ingestion of Lard in Treatment of Eczema and Allied Dermatoses: Clinical and Biochemical Study, Arch. Dermat. & Syph. **44**:849 (Nov.) 1941.

186. Burr, G. O.: Significance of the Essential Fatty Acids, Federation Proc **1**:224, 1942.

2 or 3 teaspoonfuls of lard each day for a month. He describes the observation of low iodine numbers, which indicate that the amount of unsaturation of the serum lipids is at a low level. The scaly skin of calves, chicks and dogs which developed when fat was restricted was accompanied with low iodine indexes of the blood serum, and similar results were seen in eczema. Fats have a sparing action on other food elements, especially on pyridoxine (vitamine B_6), as well as on vitamin A. The nutritive function of the fatty acids affects the kidneys, as well as the skin. In the meantime di Sant'Agnese and Larkin[187] observed that the absorption of vitamin A was impaired in 4 patients with severe eczema who also had severe eosinophilia—with up to 25 and 35 per cent of cosinophils—and severe malnutrition.

More recently three new and good papers have been published. Hansen and his co-workers[188] observed 225 patients with eczema. Studies of the serum lipids were made in 171 patients, mostly infants and children, and the iodine index was observed to be below the mean value for normal persons of the same age. When lard, in doses of 4 teaspoonfuls a day, was fed to 148 of these children, the clinical response was good in 60 (40 per cent) and fair in 51, or 35 per cent, and in these improved patients the iodine indexes became larger, in proportion to the degree of improvement. The authors add, however, that in patients treated with coal tar, with a change in diet, that the iodine indexes also showed a rise. Frazier and Small[189] present a comprehensive study of all "eczema," the relation to allergy and the biochemistry of cutaneous lesions in general. Vesicants, like the arsenic compounds, are harmful, because once having penetrated the outer keratin layer, or having reached the skin through the blood stream, they interfere with various tissue enzymes, so that they disturb the normal process by which sugar and other foods are absorbed by the cells of the skin. They suggest that in eczema the disturbed lipid metabolism of the skin interferes with nutrition of the skin and causes trouble. Stoesser[190] notes that soy beans contain unsaturated fatty acids and that soy bean milk is good for children with eczema. He treated 31 patients with soy bean milk and observed the iodine indexes to be low at the start of treatment and much higher later. In the discussion of Stoesser's paper, it was pointed out that fever improves eczema and

187. di Sant'Agnese, P. A., and Larkin, V. deP.: Vitamin A Absorption in Infantile Eczema, Proc. Soc. Exper. Biol. & Med. **52**:343, 1943.

188. Hansen, A. E.; Knott, E. M.; Wiese, H. F.; Shaperman, E., and McQuarrie, I.: Eczema and Essential Fatty Acids, Am. J. Dis. Child. **73**:1 (Jan.) 1947.

189. Frazier, C. N., and Small, A. A.: Allergic Dermatitis: A View of Its Immunologic and Biochemical Implications, Am. J. Med. **3**:571, 1947.

190. Stoesser, A. V.: Influence of Soy Bean Products on the Iodine Number of the Plasma Lipids and the Course of Eczema, J. Allergy **18**:29, 1947.

that at the same time this fever lowers the iodine index. The discrepancy is difficult to explain, unless there be a mobilization of lipids in the skin at the expense of those in the circulating blood, but there is no support for this belief.

In the winter of 1947-1948 my associates and I observed 4 patients with "atopic eczema" or "neurodermatitis" who were virtually "cured" after taking 4 tablespoonfuls of lard, either cold and used like butter on bread or warm and liquid and poured onto bread, potato or vegetables. The improvement began in a few days, and the skin was clear within two weeks. Needless to say, the same treatment for other patients has had no such beneficial effect. Does this mean that there are different types of cases: those in which there is and those in which there is not response to unsaturated fatty acid? A carefully made clinical study might answer the question and help to explain the doubts and the discrepancies in the literature.

In the meantime, Engman and MacCardle[191] have declared that in albino rats fed on a diet deficient in magnesium lesions developed similar to those of neurodermatitis. So far no one has paid attention to the possibility of a deficiency of something else besides unsaturated fatty acid in eczema in human beings, and that is a challenging thought.

SUMMARY AND CONCLUSIONS

This review describes progress in several directions. The concept of an "asthmatic state" as a constitutional factor, which explains the tendency in predisposed persons to development of one or other of the allergic diseases, as apposed to some other chronic disturbance, would appear to be supported. In more than half of this group, the antigen-antibody mechanism of allergy provided the exciting cause for the production of symptoms. In the other half, however, the exciting cause was not allergy: the causes included infections, and depletion, the latter resulting from stress and strain of various kinds of the soma or of the psyche.

The theory that each of these exciting factors liberates a poison (H substance) which is directly responsible for the symptoms appears necessary from the clinical point of view, and with respect to the antigen-antibody reaction, the evidence in human beings as well as in animals, shows that histamine is at least an important element in the poison. In the cases of infections and of depletion, the evidence that histamine is released is not too clear, but, at least, it is known that other factors besides the antigen-antibody reaction can release this histamine.

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191. Engman, M. F., Jr., and MacCardle, R. C.: A New Approach to the Problem of a Disseminated Neurodermatitis, Arch. Dermat. & Syph. **46**:337 (Sept.) 1942.

Selye's discussion of the "diseases of adaptation" appears to have an important and direct bearing on this subject.

The term "release," as applied to histamine, is good, for there is real evidence that this substance is present in many cells and tissues of the body and can move from its bound state in the tissues into an unbound state in the blood plasma. As Rose has explained, this movement can be demonstrated in a number of laboratory experiments. So far, however, it is not known how extensively it occurs in patients with asthma or urticaria, and the question needs study. It has now become clear that measures of the total histamine, which include both its bound and its free forms, are not helpful to the understanding of the process.

The fact that the antihistaminic drugs, which are so effective in neutralizing histamine when tested in direct experiment, are not more effective in the treatment of all allergic diseases has two implications: First, the discrepancy confirms the suspicion that histamine, by itself, does not constitute all of the mediating poison, and, second, the variation in the effect of the drugs suggests that not all of the clinical manifestations of allergy have precisely the same basic mechanism.

The pathologic aspects of the allergic diseases is understood better than it has previously been, thanks largely to the work of Rich, and as a result, attention has been directed to studies of the blood vessels, on the one hand, and to studies of the connective tissue, the collagen, on the other. The lesions observed in experiments with foreign serum in animals, as well as those seen in patients at autopsy, has led to a much wider appreciation of the mechanisms of allergy in clinical medicine as well as to a broader concept of allergy itself. The fact that Selye could produce lesions of similar, if not identical, character by treating his animals with adrenocortical steroids is in accord with the concept that stress and strain (depletion) is sufficient to explain the symptoms.

With even greater assurance, I can repeat that, "all is not allergy that wheezes" and can say, with equal assurance, that in many cases "the treatment of the patient is more important than the treatment of his disease."

Dr. Bram Rose of Montreal and Dr. Anne Forbes of Boston gave suggestions in the preparation of this paper.

GASTROENTEROLOGY

A Review of the Literature from July 1946 to July 1947

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Concluded from page 598

SMALL INTESTINE

Motility.—In studies by Cantoni and Eastman [304] on the responsiveness of the isolated guinea pig intestine, maximal contractions obtained in response to a large dose of histamine, acetylcholine, pilocarpine, barium chloride and "mecholyl chloride" were followed by temporary depression. On the other hand, a maximal contraction in response to large doses of potassium chloride did not result in a decreased contractility. A small increase in the potassium-calcium ratio of the perfusion fluid, such as is obtained by doubling the potassium content of Tyrode solution, was sufficient to neutralize the effect of large doses of histamine, acetylcholine, pilocarpine and barium chloride.

B-dimethylaminoethyl benzilate hydrochloride abolished the activity of exteriorized loops of dog intestine to a degree commensurate with the dosage of the drug, peristalsis being inhibited somewhat longer than rhythmic segmentation.[305] Dibutoline sulfate, a new synthetic antispasmodic drug, proved to be effective in alleviating the pain accompanying the smooth muscle spasm in a few cases of ulcerative colitis, spastic colitis, pylorospasm and premenstrual cramps.[306] Dryness of the mouth was the only side reaction noted.

A series of roentgenograms taken after ingestion of 100 cc. of a feeding mixture with barium demonstrated that the material is transported aborally at a rate sufficient to permit its routine administration as early as twenty-four hours after operation.[307]

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304. Cantoni, G. L., and Eastman, G.: On the Response of the Intestine to Smooth Muscle Stimulants, J. Pharmacol. & Exper. Therap. **87**:392-399, 1946.

305. Wakim, K.; Powell, C. E., and Chen, K. K.: The Effects of B-Dimethylaminoethyl Benzilate Hydrochloride on Intestinal Activity, Gastroenterology **7**:213-217, 1946.

306. Cummins, G. M.; Marquardt, G. H., and Grossman, M. I.: Report of a Preliminary Clinical Trial of Dibutoline: A New Antispasmodic Drug, Gastroenterology **8**:205-207, 1947.

307. Rosenak, S., and Hollander, F.: Early Postoperative Motor Response of the Small Intestine to Jejunal Feedings, S. Clin. North America **27**:345-354, 1947.

Measured amounts of fatty acids mixed with a standard dog food (Pard) were fed to dogs.[308] Diarrhea resulted from the feeding of diets containing caprylic, caproic or butyric acids or the glycerides of each. Constipation followed feedings of stearic acid or tristearin.

Gregory [309] recorded intestinal tone and motility of Thiry-Vella loops of the upper jejunum in dogs with nausea and vomiting produced by the subcutaneous injection of doses of apomorphine varying from 0.02 to 0.10 mg. per kilogram of body weight. The first signs of nausea were accompanied with a rapid inhibition of intestinal tone and motility, followed by an equally rapid increase in tone maintained for several seconds before the development of retching; subsequently, the original tone and motility were regained. The response was abolished by denervation of the mesenteric pedicle to the loop. According to the author, these observations suggest that the response is of nervous origin and probably results from the excitation of central autonomic mechanisms.

Absorption.—Moseley and Chornock [310] studied the absorption of 10 per cent galactose from the upper intestine in 6 normal persons and in 5 with thyrotoxicosis and found that the thyrotoxic patient does not absorb galactose faster than the healthy person. Galactemia bears no constant relation to the amount of galactose absorbed, either in the normal or in the thyrotoxic patient. Galactemia may be decreased by the previous administration of dextrose without the rate of galactose absorption being disturbed. This observation supports the views of Folin, Berglund and Bodansky that availability of glucose is the deciding factor in the retention and utilization of galactose.

Enzymes.—Koehler and his associates,[311] studying the effect of cigaret smoking on the rate of flow and the concentration of the amylolytic, protolytic and lipolytic enzymes of the digestive secretions in man as obtained by transduodenal drainage, noted no significant changes.

Gas.—The average content of gas in the gastrointestinal tract of male subjects was estimated as approximately 1 liter, with variations throughout the day.[312] Defecation produced no appreciable reduction. The

308. Wikoff, H. L.; Marks, B. H.; Caul, J. F., and Hoffman, W. F.: Some Effects of High Lipid Diets on Intestinal Elimination: IV. Saturated Fatty Acids, Am. J. Digest. Dis. **14**:58-62, 1947.

309. Gregory, R. A.: Changes in Intestinal Tone and Motility Associated with Nausea and Vomiting, Am. J. Physiol. **105**:58-65, 1946.

310. Moseley, V., and Chornock, F. W.: Intubation Studies of the Human Small Intestine: XXV. The Absorption of Galactose from the Intestine of Normal Individuals and Thyrotoxic Patients, J. Clin. Investigation **26**:11-17, 1947.

311. Koehler, A. E.; Hill, E., and Marsh N.: The Effect of Cigarette Smoking on Malnutrition and Digestion, Gastroenterology **8**:208-212, 1947.

312. Blair, H. A.; Dern, R. J., and Bates, P. L.: Measurement of Volume of Gas in the Digestive Tract, Am. J. Physiol. **149**:688-707, 1947.

amount of flatus passed by rectal tube in subjects on army K rations for a six day period varied from 12 to 340 cc. daily. With normal diets, the quantity of flatus averaged 200 cc. When soy bean was employed as the principal protein, amounts up to 2,600 cc. were passed daily. Large amounts of gas are passed when the motility of the intestine is high. Swallowed nitrogen may be almost completely absorbed if the motility of the intestine is low. The formation of gas from malted milk in the obstructed bowel of cats is significantly depressed by "sulfathaladine" and "sulfamethazine" (2-sulfanilamido-4, 6-dimethylpyrimidine).[313]

Meckel's Diverticulum.—In an excellent paper Kittle, Jenkins and Dragstedt [314] discuss the history, embryology, anatomy, pathologic processes, heterotopia, relation to other congenital anomalies and sex incidence of the diverticulum of Meckel. Two new cases of uncomplicated patent omphalomesenteric duct and 1 case in which prolapse occurred are presented. Four instances of peptic ulcer in Meckel's diverticulum are reported by Lund.[315]

In a series of 61 cases the highest incidence occurred during the second decade.[316] The main presenting symptom was abdominal pain. A preoperative diagnosis of appendicitis was made in 60 per cent; a correct clinical diagnosis was made in 12 per cent. Gastric mucosa was present in 24.6 per cent. Obstruction of the small bowel occurred in 5 of 22 cases reported by Haber.[317] Intestinal hemorrhage,[318] recurrent abdominal colic caused by torsion of the pedicle [319] and adenocarcinoma arising in a diverticulum [320] are reported.

Congenital Stenosis.—Two cases of congenital stenosis of the small intestine with retention of nonpenetrating foreign bodies are described.[321]

313. Segel, A.; Schweinburg, F. and Fine, J.: Effect of Sulfathaladine and Sulfamethazine on Gaseous Distention in the Obstructed Small Intestine of Cats, Proc. Soc. Exper. Biol. & Med. **63**:17-18, 1947.

314. Kittle, C. F.; Jenkins, H. P., and Dragstedt, L. R.: Patent Omphalomesenteric Duct and Its Relation to the Diverticulum of Meckel, Arch. Surg. **54**:10-36 (Jan.) 1947.

315. Lund, J.: Peptic Ulcer in Meckel's Diverticulum, Bibliot. f. læger **138**: 149-174, 1946.

316. Howell, L. M.: Meckel's Diverticulum: A Consideration of the Anomaly, with a Review of Sixty-One Cases, Am. J. Dis. Child. **7**:365-377 (April) 1946.

317. Haber, J. J.: Meckel's Diverticulum, Am. J. Surg. **73**:468-485, 1947.

318. Hanet, E.: L'hémorrahgies intestinales grave chez un enfane de douze ans: Ulcère du diverticule de Meckel, Rev. méd. Liège **2**:59-62, 1947. Girard, M.: L'hémorrhagie de l'ulcère, du diverticule de Meckel, J. de méd. et chir. prat. **117**:179-189, 1946.

319. Ingber, E.: Colicos abdominales por torsion decidivante del pedunculo de un diverticulo de Meckel degenerado, Rev. méd. de Córdoba **35**:530-591, 1946.

320. Costich, K. J., and McNamara, W. L.: Carcinoma of Meckel's Diverticulum, Ann. Surg. **124**:503-507, 1946.

321. Williams, M.: Congenital Stenosis of Small Intestine with Retention of Non-Penetrating Foreign Bodies: Report of Two Cases, Ann. Surg. **124**:492-496, 1946.

Rupture.—Kornblith [322] describes a case in which a 35 year old white man kicked in the abdomen eight hours previously but presenting no evidence of external trauma was found to have a rupture of the jejunum and generalized peritonitis due to Bacillus welchi, B. coli and the enterococcus. Closure of the perforation and chemotherapy resulted in recovery.

Perforation.—Twenty-two consecutive cases of perforation of the ileum were observed in a series of 1,077 cases of enteric fever; 11 of the patients were under observation when perforation occurred, and 11 were ambulatory[323] Perforation occurred early, usually within eleven days after the onset of illness. Pain was the predominant early symptom, usually generalized or near the umbilicus. Pelvic visceral irritation was manifested in 4 patients by dysuria and rectal tenesmus. Persistent diarrhea occurred only once. Perforation occurred at an average of 27.5 cm. from the ileocecal junction. Five deaths occurred among the ambulant patients and 7 in the nonambulant group, an over-all mortality of 55 per cent.

High Altitude Bleeding.—Severe intestinal hemorrhage occurred during exposure to low atmospheric pressure in the course of a simulated flight at high altitude.[324]

Regional Enteritis.—A corrugated steel clamp was applied momentarily to isolated segments of the small bowel of mongrel dogs.[325] The animals survived the initial injury without ill effects; slight loss in weight and occasional bloody stools were observed. When they were killed three to seven months later, the findings consisted of fibrous and omental adhesions, particularly on the antimesenteric side, round cell infiltration in the submucosa, lymphoid follicular hyperplasia and fibrous tissue proliferation.

Garlock [326] emphasizes the following five main types of symptoms in regional ileitis: (*a*) acute manifestations, usually erroneously diagnosed as indicative of acute appendicitis, (*b*) enteric symptoms, with the triad of foul, nonbloody diarrhea and cramps, weight loss and anemia (fever may be present, depending on the extent of the disease outside the bowel wall), (*c*) obstructive symptoms, (*d*) symptoms caused by involvement of adjacent viscera, such as vesical fistulas, and (*e*) the presence of external fecal fistulas. The lowest mortality and the best

322. Kornblith, B. A.: Rupture of the Jejunum Without Evident External Trauma, New York State J. Med. **46**:1940-1941, 1946.

323. Dunkerley, G. E.: Perforation of the Ileum in Enteric Fever: Notes on Twenty-Two Consecutive Cases, Brit. M. J. **2**:454-457, 1946.

324. Schier, W. W.: Massive Gastrointestinal Bleeding Following Exposure to Low Pressure, New England J. Med. **236**:898-901, 1947.

325. Spellberg, M. A., and Ochsner, A.: The Role of Trauma as a Possible Etiologic Factor in Regional Enteritis: The Effect of Non-Penetrating Trauma on the Small Intestine of Dogs, Am. J. M. Sc. **213**:579-584, 1947.

326. Garlock, J. H.: The Present Status of the Problem of Regional Ileitis, Am. J. Surg. **72**:875-878, 1946.

late results are obtained when ileotransverse colostomy is performed, with exclusion of the ileum proximal to the upper limits of the diseased segment. After simple short-circuiting operations, complete recession of the nodal involvement has repeatedly been demonstrated at secondary laparotomy. Among nearly 100 patients so treated there have been no deaths, and follow-up studies have shown "the smallest percentage of recurrences." Homb [327] describes the pathologic appearance in the acute form of the disease.

Pratt and Ferguson [328] report 9 cases of what they choose to call "cicatrizing enterocolitis." The cause is thought to be some infection, most likely originating in the appendix, causing a "morbid" lymphadenitis in the mesenteric glands, with a subsequent or concurrent lymphedema. Appendectomy is recommended when laparotomy is performed in the early stages presumably for acute appendicitis. Crushing of the stump is to be avoided. Patients seen in the "ulcerative colitis stage" are treated medically for three months provided no significant stenosis has occurred. The disease subsides spontaneously in a high percentage of cases. The surgical procedure of choice for patients who are not improving is a by-passing operation, with exclusion and anastomosis of loops entirely free of the disease as shown by local examination and by the absence of enlarged mesenteric nodes. The mortality rate after resection, indicated in the obstructive stage, depends on the extent.

Extensive involvement of the ileum, cecum, ascending colon and transverse colon is described,[329] and other interesting cases are reported.[330] Intestinal obstruction and abscess secondary to regional ileitis were diagnosed in the seventh month of pregnancy in a case described by Babson.[331]

Tuberculosis.—In 6 instances of intestinal tuberculosis in patients with moderately extensive pulmonary disease, routine treatment, consisting of a low roughage diet, administration of vitamins A, C and D, and 5 cc. of 20 per cent calcium gluconate intravenously three times a week and the cautious use of ultraviolet rays, seemed to be helpful; proper treatment of the primary lesion in the lung was of the utmost importance.[332]

327. Homb, A.: On Acute Regional Enteritis, Acts chir. Scandinav. **4**:343-357, 1946.

328. Pratt, G. H., and Ferguson, L. K.: Cicatrizing Enterocolitis, Am. J. Surg. **73**:28-36, 1947.

329. Cash, I. I.; Pilcher, L. S.; Rappoport, A. E., and Barker, W. A.: Regional Ileitis Involving the Ileum, Cecum, Ascending Colon and Transverse Colon, Ann. Int. Med. **25**:351-362, 1946.

330. Gogniaux, P.: Un cas a'ileite regionale, Acta clin. belg. **1**:340-348, 1946. Fusaro, W. J.: Regional Ileitis, Am. J. Surg. **73**:720-724, 1947.

331. Babson, W. W.: Terminal Ileitis with Obstruction and Abscess Complicating Pregnancy, New England J. Med. **235**:544-547, 1946.

332. Keers, R. T.: Intestinal Tuberculosis: Some Observations, Brit. J. Tuberc. **41**:3-37, 1947.

Steatorrhea and Sprue.—Steatorrhea is defined by Ricketts, Maimon and Knowlton [333] as an increase in the total amount of fecal fat above the normal of 10 to 20 Gm. per day or in the percentage of fat in the dry stool, the upper limit being about 20 per cent. The types of steatorrhea are listed as pancreatic, "idiopathic," including tropical and nontropical sprue and celiac disease, and miscellaneous, including obstruction of the mesenteric lymphatic vessels, intestinal lipodystrophy and lipogranuloma, gastrojejunocolic fistula, regional enteritis and sequelae of protozoan and bacillary dysenteries. Certain laboratory signs such as anemia, hypoproteinemia, hypocalcemia and impairment of fat absorption are common to most cases of steatorrhea, whatever the cause, and thus are of little help in the differential diagnosis. Likewise, determination of gastric acidity, serum amylase content, pancreatic enzymes in the intestinal contents, fecal nitrogen and the partition of fecal fat between neutral fat, fatty acids and soaps has been of no aid in distinguishing one type of steatorrhea from another. The first diagnostic step is a search for pathogenic organisms in the stools, since diarrhea on a parasitic or bacterial basis may result in excessive fat excretion. The next is a careful roentgenologic study of the gastrointestinal tract, including a roentgenogram of the abdomen designed to reveal calcification in the region of the pancreas. If the glucose tolerance curve is not flat and if there is no response to treatment with adequate amounts of crude liver extract (and folic acid), a condition other than "idiopathic" steatorrhea is likely, and if other studies have been unfruitful, surgical exploration may be indicated.

Shane and Deyke [334] believe that there are two etiologic factors in sprue; first, the deficiencies of "extrinsic" or "intrinsic" factors as proposed by Castle, Rhoads and Lawson; second, mechanical factors preventing absorption from the small bowel, such as lymphatic obstruction, and operative disturbances of anatomic relationships. Wingfield [335] concludes that the syndrome is due to a deficiency of some hypothetic substance contained in certain crude liver extracts. The course of sprue as observed in 680 cases [336] consisted in the appearance of diarrhea, anorexia and vomiting, usually in that order, followed by asthenia, loss of weight and dehydration. In the majority of cases (63 per cent) diet alone produced a remission. The symptoms of beginning remission were glossitis, cheilosis and angular stomatitis. Glossitis was present in 90

333. Ricketts, H. T., Maimon, S. N., and Knowlton, K.: Steatorrhea, M. Clin. North America **31**:125-133, 1947.

334. Shane, S. J., and Deyke, V. F.: Observations on the Sprue Syndrome, Canad. M. A. J. **55**:448-450, 1946.

335. Wingfield, A. L.: Some Observations on the Etiology and Treatment of Sprue, Proc. Roy. Soc. Med. **39**:519-522, 1946.

336. Keele, K. D.: A Study of the Onset and Cyclic Development of the Sprue Syndrome, Brit. M. J. **2**:111-114, 1946.

per cent of the cases, usually during the transitional stage from relapse to remission or vice versa. Abdominal distention appeared, together with gain in weight, as the nausea, vomiting and diarrhea subsided. Scaling of the skin and loss of hair frequently accompanied the remission. Despite diets designed to contain 5 to 10 mg. of nicotinic acid and 3 mg. of riboflavin daily, an exacerbation of glossitis, which cleared in fourteen days without alteration in diet developed in 2 patients; in others the glossitis subsided without other treatment. Glossitis was minimal in the remissions induced with liver therapy. The degree of anemia was usually not severe in early cases, only 24 per cent of 600 patients having values for hemoglobin below 12 Gm. per cent. Macrocytic anemia was observed initially in 26 per cent of 80 cases. Macrocytosis without anemia was noted in 30 per cent, normal blood cell counts in 35 per cent and hypochromic anemia in 9 per cent. In remission, the change uniformly was from macrocytic anemia to macrocytosis only and then to normal blood counts. According to the author the return of the blood picture to normal always follows the return to normal weight

The development of the sprue syndrome in 3 servicemen who had returned from the Southwest Pacific theater is reported by Olson and Layne.[337] It is pointed out that sprue may develop in persons who have previously had diarrhea of bacillary or parasitic origin, with sufficient damage to the intestinal mucosa to impair absorption of essential food substances.

Diarrhea was the initial symptom in 1,069 patients with the sprue syndrome among Italian prisoners of war in India.[338] Ninety per cent presented signs of secondary deficiencies of the vitamin B type. Pigmentation of face, hands and abdomen, hypotension and mild hypochromic anemia were noted in the second week of the disease. A lowering of serum protein levels, edema and macrocytic hyperchromic anemia developed in untreated patients and in those in whom the diarrhea was not controlled within four or five weeks after the onset. Laboratory studies on 253 patients revealed low serum calcium levels, flat curves for the oral glucose tolerance test and urobilinogen in the urine. A 1,000 calorie, high protein, low fat diet was given during the acute phase of the disease, with an increase of protein for patients in whom severe anemia developed. Vitamins and liver extract were employed. Most patients recovered promptly. Twenty-three had relapses during every rainy season. In 4 cases the condition became chronic, and in 5 it terminated in aplastic anemia.

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337. Olson, S. W., and Layne, J. A.: Sprue as a Sequence to the War's Migration of Military Personnel, Gastroenterology **8**:221-227, 1947.

338. Stefanini, M.: Observations on a Series of Cases of Sprue in a Prison Camp in India, Gastroenterology **8**:729-734, 1947.

Black, Fourman and Trinder,[339] studying the feces in cases of sprue, noted that many patients seemed to respond well to sulfonamide compounds, which suggested the concomitant presence of bacillary infections or the prevalence of sulfonamide-sensitive organisms which though ordinarily not pathogenic assume pathogenic properties when there is an abnormal intestinal tract. The irritant character of the fatty stools seems to be due to soluble soaps and not to acidity. For detection in questionable cases, 100 Gm. of fat should be administered daily and stools examined over a four to ten day period, since the fat content varies. A high residue diet will lead to low values for the percentage of fat in dried stool. In the normal person the quantity of fat excreted daily should not exceed 10 Gm.

Bacteriologic and parasitic studies in 25 cases of tropical sprue[340] disclosed Trichuris trichiura, Ascaris lumbricoides, Necator americanus and a wide variety of organisms, the butyribacillus being found in 72 per cent. Though the blood picture and clinical manifestations improved with folic acid therapy, no significant change was noted in the parasitic and bacterial contents of the bowel as determined by proctoscopic swab.

Preliminary investigations of the mechanism of fat digestion were carried out on 10 patients with tropical sprue and on 8 normal subjects who served as controls.[341] With the use of a radiopaque double-lumened Miller-Abbott tube, intestinal contents were collected before and after ingestion of 25 cc. of olive oil. The secretions of controls appeared as uniformly suspended bile-stained emulsions; those of the patients with sprue contained whitish threads and clumps suspended in clear bile-stained fluid. Microscopically, all samples showed numerous fat droplets. In the samples from the controls these were evenly dispersed: in those from the patients with sprue they were aggregated in clumps. Stains indicated the presence of fatty acids and some well emulsified unsplit fat. It appears, therefore, that in the sprue syndrome fat is emulsified and, as would be expected from analysis of stool fat, hydrolyzed. The abnormality lies in either aggregation into clumps and threads of the fatty material or the failure to disperse such aggregations if they occur as a transitory phase of normal digestion. To assess the possibility of dispersing these clumps and threads, three specimens were incubated at 37 C. for four hours with fasting succus entericus which was (1) normal, (2) normal and mixed with ox bile, (3) obtained from patients with mild

339. Black, D. A. K.; Fourman, P., and Trinder, P.: Faeces in Sprue, Brit. M. J. **2**:418-420, 1946.

340. Milanes, F.; Curbelo, A.; Rodriguez, A.; Kouri, P, and Spies, T. D.: A Note on Bacteriological and Parasitic Studies of the Intestinal Contents of Patients with Sprue, Gastroenterology **7**:306-313, 1946.

341. Smart, G. A., and Daley, R.: Fat Digestion in Sprue, Studied by Intestinal Intubation, Lancet **2**:159-160, 1946.

sprue, (4) obtained from patients with mild sprue and mixed with ox bile, (5) obtained from patients with severe sprue and (6) obtained from patients with severe sprue and mixed with ox bile. Good dispersal of the clumps was observed in specimen 1, and moderate dispersal in specimen 3 and no dispersal in specimen 5. Addition of ox bile helped. In general, there is a rough correlation between the clinical severity of the disease and the degree of clumping. The investigations suggest that the clumps and threads consist mainly of fatty acids both finely dispersed and in droplet form bound in a mucin-like matrix. The problem remains whether the digestion of mucus is impeded in sprue because the mucus itself is abnormal or because the digestive juices lack mucus-splitting ferment.

Among 20 patients with sprue the lowest plasma tocopherol values occurred in persons who had suffered a relapse or who were experiencing early remission.[342] During relapse, a maximum rise in serum concentration of tocopherols of 0.09 mg. per hundred cubic centimeters was noted after an oral dose of 600 mg. of mixed tocopherols, in contrast to the mean maximal rise of 0.37 mg. in 7 healthy adults. In 17 patients experiencing a remission of sprue after a long period of treatment with liver extract the tocopherol levels were found to be essentially normal.

Between 5 and 10 per cent of patients with sprue acquired in military service have had low blood pressure, asthenia and signs of peripheral circulatory failure.[343] Ten of 41 patients had low values for serum sodium and serum chloride and, in some instances, a plasma volume which was low in relation to the body weight. The diminished serum sodium content was most pronounced. Studies of a typical patient revealed abnormal loss of sodium and a lesser degree of loss of chloride in the feces; in the urine chloride was lost and sodium was rapidly conserved. When the patient was on a high salt intake, sodium and chloride were retained, the blood pressure improved and signs of dehydration disappeared. The symptoms were attributed to salt deficiency modified by some degree of acidosis due to the preponderant loss of sodium over chloride. Serum potassium was not increased, and conservation of base by the kidneys was adequate. Loss of electrolyte in the copious watery stools probably accounts for the salt deficiency.

Harrison and others,[344] studying the potassium deficiency in a case of lymphosarcoma and the sprue syndrome, found an excessive fecal loss of potassium.

342. Darby, W. J.; Cherrington, M. E., and Ruffin, J. M.: Plasma Tocopherol Levels in Sprue, Proc. Soc. Exper. Biol. & Med. **63**:310-312, 1946.

343. Black, D. A. K.: Salt Deficiency in Sprue, Lancet **2**:671-675, 1946.

344. Harrison, K. E.; Harrison, H. C.; Tompsett, R. R., and Barr, D. P.: Potassium Deficiency in a Case of Lymphosarcoma with the Sprue Syndrome, Am J. Med. **2**:131-143, 1947.

An unusual case of nontropical sprue in a 15 year old boy is presented by Schein.[345] Death occurred from necrosis of the liver on the second day after his admission to the hospital. The clinical manifestations included diarrhea, bulky pale yellow stools containing a large amount of fatty acid crystals and neutral fat globules, fever, lymphadenopathy, acidosis, hypoprothrobinemia, hypocalcemia and tetany. Autopsy revealed an extensive and severe parenchymal degeneration of the liver, with fatty infiltration and dissociation of the hepatic cells, and an unidentifiable hyaline material disposed mainly as villous tip bands over the upper portions of the villi of the small intestine, whose characteristic deformation was "clubbing and mushrooming." In a second case also, that of a 71 year old man who presented a clinical picture suggestive of sprue, microscopic examination disclosed, though to a lesser extent, villous clubbing and hyaline villous tip bands.

Garcia Lopez and others[346] report rehabilitation of 18 patients with sprue treated with folic acid in daily doses of 25 to 200 mg. A daily oral dose of 10 mg. proved adequate in a series reported by Suarez and others,[347] small daily doses being more effective than fifty times as much given in a single dose. A daily dose of 20 mg. with an adequate diet produced better results than larger doses with an inadequate diet. An adequate maintenance dose seemed to be between 5 and 25 mg. per day.

Striking improvement in the roentgen appearance of the small bowel following the oral administration of 10 mg. of folic acid daily[348] was evidenced by a return to normal intestinal motility and by the establishment of a continuous column of barium not interrupted by segmentation or fragmentation; no change was detected in an untreated control patient.

A dramatic improvement occurred both in the blood picture and in intestinal absorption after synthetic folic acid was given to 2 previously untreated patients.[349] Two patients with sprue of long duration previously treated by administration of liver were improved subjectively, but little or no effect was observed on the blood.

Folic acid therapy failed to produce a significant rise in the red blood cell count or to restore the blood level and the hematologic picture to

345. Schein, J.: Syndrome of Non Tropical Sprue with Hitherto Undescribed Lesions of the Intestine, Gastroenterology **8**:438-460, 1947.

346. Garcia Lopez, G.; Spies, T. D.; Menendez, J. A., and Lopez Toca, R.: Folic Acid in the Rehabilitation of Persons with Sprue, J. A. M. A. **132**:906-911 (Dec. 14) 1946.

347. Suarez, R. M.; Spies, T. D., and Suarez, R. M., Jr.: The Use of Folic Acid in Sprue, Ann. Int. Med. **26**:543-677, 1947.

348. Hernandez Beguerie, R. L., and Spies, T. D.: Roentgenologic Studies on the Effect of Synthetic Folic Acid on the Gastrointestinal Tract of Patients with Tropical Sprue, Am. J. Roentgenol. **56**:337-342, 1946.

349. Morrison, R. J. D., and Johnston, C. R.: Treatment of Tropical Sprue with Folic Acid, Lancet **1**:636-637, 1947.

normal in 9 of 10 patients; in 7 adults the diarrhea was controlled and clinical improvement resulted, whereas no significant benefit was observed in 3 patients with celiac disease. Folic acid did not improve fat absorption as estimated by fat balance tests on 5 of 6 patients treated by Davidson and his associates;[350] on the other hand, Tegalaers and Weyers[351] noted improvement in fat absorption in 7 children treated by daily oral administration for thirty days of 10 mg. of folic acid.

Intestinal Lipodystrophy.—Pemberton and others[352] describe 3 additional cases of intestinal lipodystrophy (Whipple's disease); a fourth case is reported by Escudero and his associates.[353]

Intussusception.—Sixty-eight per cent of 95 infants and children with acute intussusception were under 1 year of age.[354] In 82.1 per cent no cause was found for the intussusception. A correct clinical preoperative diagnosis was made in 93 of the 95. The majority of intussusceptions occurred at the ileocecal junction. Resection resulted in a mortality rate of 42.8 per cent for 14 patients. The greatest single factor responsible for the high mortality rate was the prolonged duration of symptoms.

Subacute ileoileal intussusception occurring at a distance of over 3 feet (91 cm.) proximal to the ileocecal valve is reported by Tiscenco.[355] Operation confirmed the roentgenologic diagnosis. Intussusception occurred after intubation with a Miller-Abbott tube.[356] Retrograde intussusception of the large bowel into the small bowel, with chronic obstruction, was produced by a carcinoma of the cecum.[357] Finestone[358] reports an instance of intussusception of the excluded distal loop of ileum after ileocolostomy, with spontaneous expulsion per annum of the sequestrated intussusceptum.

Intestinal Obstruction.—Harper and Lemmer[359] produced simple intestinal obstruction by inverting both ends of the divided small bowel in

350. Davidson, L. S. P.; Girdwood, R. H., and Innes, E. M.: Folic Acid in the Treatment of the Sprue Syndrome, Lancet **1**:511-515, 1947.

351. Tegalaers, W. H. H., and Weyers, H. A.: Influence of Folic Acid on Symptoms of Celiac Disease, Maandschr. v. kindergeneesk. **15**:107-109, 1947.

352. Pemberton, J. deJ.; Comfort, M. W.; Fair, E. and Zaslow, J.: Intestinal Lipodystrophy (Whipple's Disease), Surg., Gynec. & Obst. **85**:85-91, 1947.

353. Escudero, P.; Mosto, D., and Landabure, P. B.: Lipodistrofia intestinal de Whipple, Rev. Asoc. méd. argent. **60**:795-803, 1946.

354. Oberhelman, H. A., and Condon, J. B.: Acute Intussusception in Infants and Children, S. Clin. North America **27**:3-22, 1947.

355. Tiscenco, E.: Subacute Ileo-Ileal Intussusception in the Adult, Brit. J. Radiol. **19**:374-380, 1946.

356. Nichols, H. M.: Intussusception Occurring After Intubation of Small Intestine, Northwest Med. **45**:924-925, 1946.

357. Thorek, P., and Lorimer, W. S., Jr.: Retrograde Intussusception, J. A. M. A. **133**:21-23 (Jan. 4) 1947.

358. Finestone, E. O.: Intussusception of Excluded Distal Ileum with Spontaneous Expulsion per Anum of Sequestrated Intussussceptum, Surgery **21**:34-42, 1947.

10 dogs at levels of 20 cm. below the pylorus, 100 cm. below the ligament of Treitz and 5 cm. proximal to the ileocecal valve. Water was given ad libitum. The average survival rate for animals with high obstruction was 9 days, for those with midileal obstruction 5.5 days and for dogs with low ileal obstruction 7.7 days, which indicates that, contrary to common belief, the higher the obstruction the greater the longevity. The main causes of symptoms and deaths appeared to be loss of fluid and electrolytes, distention, necrosis and ulceration of the intestinal wall, with possible absorption of toxins from bacteria, tissue necrosis and intestinal contents. The writers postulate that the reason human beings die of ulceration and perforation is that while fluid loss and electrolyte imbalance are easily corrected the relief of distention, which leads to necrosis and ulceration, is not so simple. Further observations showed that the normal intestinal bacteria acting on an ischemic distended bowel were responsible for ulceration and perforation and that the lower the obstruction the greater was the distention, necrosis and ulceration and the higher was the incidence of positive cultures of peritoneal and heart blood at autopsy.

In an interesting study by Blain and his associates [360] on the effect of penicillin, 10 dogs were subjected to artificial strangulation of the terminal 60 cm. of ileum by ligation of all vessels supplying this segment. Vomiting, distention, ascites and paralysis of the extremities developed in 5 animals serving as controls and given no treatment other than parenteral administration of fluids, and they died within twenty-six to thirty-six hours. The strangulated segments showed gross and microscopic evidence of ulceration, with intramural hemorrhage. The 5 animals treated with massive doses of penicillin were alive seventy-two hours later, after which time the strangulated bowel was resected; 1 died eight hours later and the other 4 recovered completely. Acute ulcerative enteritis was found in both the controls and the treated dogs. The authors conclude that the administration of massive doses of penicillin is a useful adjunct in the management of obstruction with strangulation but it does not supplant surgical intervention.

Obstruction of the small intestine due to adhesions and bands is discussed in a two hundred page monograph by Krook,[361] with particular reference to the causes of recurrence. The clinical features of obstruction of the small bowel are considered by Hunt.[362] Roentgen examina-

359. Harper, W. H., and Lemmer, R. A.: Necrosis and Ulceration of the Intestinal Wall in Simple Intestinal Obstruction: An Experimental Study, Bull. Johns Hopkins Hosp. **79**:207-228, 1946.

360. Blain, A. III; Kennedy, J. D.; Calihan, R. J., and Harkins, H. N.: Effect of Penicillin in Experimental Intestinal Obstruction, Arch. Surg. **53**:378-386 (Oct.) 1946.

361. Krook, S. S.: Obstruction of the Small Intestine Due to Adhesions and Bands, Acta chir. Scandinav., 1947, supp. 125, pp. 1-200.

362. Hunt, C. J.: Early Indications of Adhesive Small Bowel Obstruction, Am. J. Surg. **72**:865-868, 1946.

tion of the abdomen should be done early in every case of abdominal distention in which there is a possibility of a mechanical obstruction of the bowel. Levitin [363] recommends that routine roentgenograms of the abdomen include a view of the organ in the lateral decubitus position in addition to the upright view. An instance is cited wherein a roentgenogram taken at the bedside with the patient lying on the left side disclosed free air in the abdomen (perforated peptic ulcer) whereas the upright view failed to do so. The lateral view is particularly useful also in the diagnosis and differentiation of paralytic and mechanical ileus. The tendency in both conditions for the gas to rise and the fluid to seek a common level because of free communication between the loops of distended bowel is best demonstrated in the lateral views. The increased prominence of the valvulae conniventes in mechanical obstruction is best shown by such views. They often reveal more effectively than the upright position the shadows cast by the properitoneal fat pad.

Hendricks and Griffin [364] report an analysis of 352 cases of obstruction; in 168 cases the obstruction was in the small bowel, and in 184 it was in the large bowel. Adhesions were the main cause of obstruction in the small bowel, the ileum being involved in 89.4 per cent. Resection was performed in 34 per cent, with a total mortality of 27.9 per cent. Carcinoma was the cause of obstruction in the colon in 90 per cent of the cases.

Eliason and Welty,[365] in a statistical survey of 292 cases, found that the mortality was not appreciably influenced by the completeness or suddenness of the obstruction. The mortality rate was 10 per cent in 176 cases of partial obstruction and 12 per cent in 116 cases of complete obstruction. Eleven per cent of the 153 patients with acute obstruction died, as did 11 per cent of 139 with chronic obstruction. The mortality rate was 8 per cent in 184 cases involving the small bowel and 16 per cent in 114 involving the large bowel. Carcinoma probably accounts for the high mortality in the latter group. The commonest causes of obstruction were adhesions (27 per cent), malignancy (20 per cent), hernia (23 per cent), lymphopathia venereum (14 per cent) and postoperative obstructions (11 per cent). The causes were miscellaneous in 5 per cent. In 59 cases malignant growths were accompanied with obstruction, with a mortality of 34 per cent. The mortality among 13 patients with femoral hernia was 31 per cent. The mortality for patients subjected to resection was 19 per cent as compared with 11 per cent for those not operated on. The causes of death were as follows: peritonitis

363. Levitin, J.: Scout Film of the Abdomen, Radiology **47**:10-29, 1946.

364. Hendricks, W., and Griffin, W. D.: Intestinal Obstruction, S. Clin. North America **27**:51-72, 1947.

365. Eliason, E. L., and Welty, R. F.: A Ten Year Survey of Intestinal Obstruction, Ann. Surg. **125**:57-65, 1947.

in 25 per cent of the cases, carcinoma in 22 per cent, pulmonary embolism in 16 per cent, pneumonia in 13 per cent and cardiovascular-renal disease in 9 per cent. In 15 per cent death was due to other causes. The mortality was reduced by one half after the introduction and use of the Miller-Abbott tube, decreasing from 18 to 9 per cent. Improvement in surgical technic and supportive and antibiotic therapy are thought to have played a role in the reduced mortality.

Devine [366] conceives paralytic ileus as characterized by three stages. In the first stage intestinal movements are active, coordinated and responsive to stimulation; in the second, movements are incoordinated, irregular and ineffective and in the third there is a complete disappearance of intestinal movement. Morphine is stressed as a useful prophylactic, since it increases the tone and frequency of small mixing waves even though peristalsis is decreased. Barbiturates decrease peristalsis and tone. During the stage of incoordinated and ineffective movements, stimulants such as enemas or pituitary extracts are likely to increase distention and pain rather than to relieve them. It is pointed out that true paralytic (idiopathic) ileus is rare and that localized peritonitis, abscess and pockets of infection are by far the more common causes. It is further stressed that drugs, intubation, enemas and stupes do not afford relief. In cases of fully developed paralytic ileus intubation, with fluid and electrolyte replacement, is the treatment of choice. Ileostomy or jejunostomy does not "cure" paralytic ileus.

Evans and Bigger [367] emphasize the importance of early diagnosis and surgical intervention in the treatment of obstruction from strangulation. The authors recommend laporotomy if the differentiation between simple and strangulating obstruction cannot be made within twenty-four hours after the onset since the lethal factors in strangulation, namely, shock and peritonitis, may soon become irreversible.

Schwartz [368] reports the sixth case of obstruction caused by a congenital adhesive band compressing the sigmoid in a 3 day old male infant. Obstruction in 2 cases was attributed to hematoma.[369] Severe intestinal obstruction occurred twelve hours after the ingestion of barium in a case of carcinoma of the hepatic flexure.[370] Intubation was successful

366. Devine, J.: A Concept of Paralytic Ileus: A Clinical Study, Brit. J. Surg. **34**:158-179, 1946.

367. Evans, E. I., and Bigger, I. A.: Early Recognition and Management of Intestinal Strangulation, J. A. M. A. **133**:513-517 (Feb. 22) 1947.

368. Schwartz, A. R.: Mesenteric Bands Producing Intestinal Obstruction in a Three-Day-Old Infant with Recovery, Arch. Pediat. **63**:317-319, 1946.

369. Dealy, F. N., and Miceli, P. A.: Intraperitoneal Hemorrhage Complicating Simple Large Bowel Obstruction, Surgery **21**:542-545, 1947.

370. Stalker, L. K.: Barium as a Factor in Intestinal Obstruction, Am. J. Surg. **72**:756-757, 1946.

in 96 per cent of 200 cases of intestinal distention; a single-lumened tube with a mercury-weighted, balloon-tipped head was used.[371] Cecostomy and the passage of a Miller-Abbott tube through the cecostomy opening for the purpose of "back-flushing" and also for decompression of the anastomosis are recommended in the management of obstruction of the colon.[372]

Necrosis.—Jeckeln [373] describes a peculiar necrosis of the intestinal mucosa observed in thirty-five postmortem specimens and in seven surgical specimens. The fully developed process is characterized by necrosis of the mucosa, with a sloughing of the submucosa and the muscularis. Microscopic examination reveals thrombosis in the vessels of the submucosa. Hemorrhage and perforation may occur. The upper portion of the small intestine is usually the site of the severest involvement, although other portions of the small bowel and even the colon may be involved. Clinically, the onset is usually acute, with severe colicky pains in the upper part of the abdomen, usually most severe on the left.[374] Constipation is followed by bloody diarrhea. The sedimentation rate and the leukocyte count are increased. Early complications include peritonitis, paralytic ileus, diplegia or tetraplegia and Landry's paralysis as the result of capillary hemorrhages in the brain and in the spinal cord. The cause is still unknown, but dysentery, cholera or arsenical poisoning are said to have been excluded. The mortality averages about 40 per cent.

Benign and Malignant Tumors.—Sixty-five tumors of the small bowel, thirty-three of them malignant, reviewed by Botsford and Seibel [375] included eighteen adenocarcinomas, sixteen argentaffinomas, thirteen lymphosarcomas, nine lipomas, five adenomas, two leiomyomas and two fibromas. Forty-one were located in the ileum. Palpable masses were rare except in cases of lymphosarcoma, being present in 11 of 13 such cases. The diagnosis depends on thorough roentgenologic investigation of the small bowel in every patient with suggestive symptoms. Cattell and Colcock [376] report five tumors of the small intestine.

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371. Cantor, M. O.; Kennedy, C. S., and Reynolds, R. P.: Use and Abuse of Intestinal Decompression Tube: A Study Based upon Two Hundred Cases, Am. J. Surg. **73**:437-449, 1947.

372. Millet, J. B.: Cecostomy and the Miller-Abbot Tube: A Report on Their Combined Use in the Preparation of the Obstructed Large Bowel for Surgery, Surg., Gynec. & Obst. **84**:1083-1086, 1947.

373. Jeckeln, E.: Intestinal Necrosis: I. Pathologic and Anatomic Aspects, Deutsche med. Wchnschr. **72**:105, 1947.

374. Ruppert, C.: Intestinal Necrosis: II. Clinical Aspects, Deutsche med. Wchnschr. **72**:108, 1947.

375. Botsford, T. W., and Seibel, R. E.: Benign and Malignant Tumors of the Small Intestine, New England J. Med. **236**:683-694, 1947.

376. Catell, R. B., and Colcock, B. P.: Tumors of the Small Intestine, S. Clin. North America **27**:644-650, 1947.

The roentgen features of sarcoma of the small intestine, according to Root,[377] are involvement of a long segment, rigidity of the wall, lack of peristalsis, ulceration and a filling defect or stenosis.

Anemia was an outstanding feature in 2 patients with an adenocarcinoma of the jejunum and a benign leiomyoma of the ileum, respectively, in whom roentgen studies did not reveal the disease.[378] Massive hemorrhage occurred in a case of jejunal leiomysarcoma.[379] The outstanding symptoms in carcinoma of the jejunum were those of chronic, progressive, intermittent obstruction.[380] A leiomyoma of the jejunum had been interpreted clinically as a duodenal ulcer.[381] Lymphoblastoma of the terminal end of the ileum was found in a soldier aged 30.[382] Two patients with malignant growths of the jejunum are alive and well six and one-half years after resection.[383] A melanosarcoma of the ileum and brain appearing five years after removal of a primary tumor from the left leg is described.[384] Tumors of this type are rare, 25 cases in all having been reported in 1945. Of these, the disease was considered primary in 9. In the case reported there were no abdominal symptoms or signs to suggest the intestinal lesion.

A solitary, sclerosed, polypoid hemangioma produced intermittent intussusception and resulted in chronic partial intestinal obstruction.[385] The patient, a 50 year old woman, complained of intermittent, colicky, epigastric pain for five years, accompanied with melena and normocytic anemia. Dilatation of the proximal end of the jejunum was demonstrated in roentgenograms.

Pneumatosis Intestinalis.—Gaseous accumulations within the wall of the intestine, known as pneumatosis cystoides intestinalis, are primarily diagnosable by roentgen study.[386] Gas shadows lying within the contour of the bowel together with inconstant filling defects of increased trans-

377. Root, J. C.: Neoplasms of the Small Intestine, Cleveland Clin. Quart. **14**:81-89, 1947.

378. Mourot, A. J., and Watkins, C. H.: Tumors of the Small Intestine, Am. J. Surg. **73**:385-389, 1947.

379. Collins, E. N., and Spencer, F.: Massive Hemorrhage Due to Leiomyosarcoma of the Jejunum, Cleveland Clin. Quart. **14**:1-6, 1947.

380. Sawyer, K. C.; Workman, C. W., and Queen, F. B.: Carcinoma of the Jejunum, Rocky Mountain M. J. **44**:287-289, 1947.

381. Marshall, S. F., and Welch, M. L.: Leiomyoma of the Jejunum, New England J. Med. **236**:95-97, 1947.

382. Galluccio, A. C.: Lymphoblastoma of the Terminal Ileum, New York State J. Med. **46**:2049-2052, 1946.

383. Connolly, E. A., and Lempka, A. W.: Jejunal Malignancy, Surgery **21**: 901-910, 1947.

384. Spier, J., and Wood, E. C.: Metastic Melanocarcinoma Involving the Small Intestine and Brain, New England J. Med. **263**:824-828, 1947.

385. Browne, D. C., and McHardy, G.: Solitary Sclerosing Hemangioma of the Jejunum, Gastroenterology **8**:665-667, 1947.

386. Lerner, H. H., and Gazin, A. I.: Pneumatosis Intestinalis: Its Roentgenologic Diagnosis, Am. J. Roentgenol. **56**:464-469, 1946.

lucency are pathognomonic. Crepitation may be noted in a distended loop of bowel on physical examination.

PARASITIC AND DIARRHEAL DISEASES

Enteric Infections.—Kirsner [387] reemphasizes the need for a constant awareness of the possible presence of bacillary dysentery, amebic dysentery and food poisoning among outbreaks of acute diarrhea. The clinical features of these diseases are reviewed, and present methods of diagnosis and therapy are described. Baird [388] discusses the causes of chronic diarrhea.

Nineteen outbreaks of epidemic diarrhea of the newborn were reported to the Massachusetts Department of Public Health from 1935 to 1945, with morbidity rates of 49 and 21 per cent for premature and full term infants respectively and mortality rates of 53 and 25 per cent.[389] Investigation revealed many inadequacies in the operation of the nurseries.

A virus or viruses rendering the intestinal mucosa vulnerable to secondary bacterial invasion is suggested by studies of acute enteritis in the Middle East.[390] Kershaw [391] regards as fallacious the tendency to attribute all nonspecific diarrheas to infection and supports the view that many are caused by sudden chilling of the abdomen.

A fatal case of acute enterocolitis resulting from administration of a markedly hypertonic alkaline enema to a 6 year old child is reported.[392] Because of mild abdominal distention and restlessness, the child was given an enema consisting of a half cup of soda (about 130 Gm.), a half cup of sugar and a half cup of salt in a quart (946 cc.) of tepid water. Within a minute after slow administration had been completed, abdominal pain, cramps and vomiting ensued, followed by coma. Nine hours later, generalized convulsions were followed by death. Autopsy revealed extensive epithelial necrosis, ulceration, congestion and leukocytic infiltration in the large bowel and to a lesser degree in the small intestine. The submucosa of the stomach was congested and edematous. An outstanding finding was the presence of early necrosis of the germinal centers of the lymphoid follicles both in Peyer's patches and in the spleen.

387. Kirsner, J. B.: Acute Enteric Infections, M. Clin. North America **31**:113-124, 1947.

388. Baird, M.: Chronic or Recurrent Diarrhea, Canad. M. A. J. **55**:273-278, 1946.

389. Rubenstein, A. D.: Epidemic Diarrhea of the Newborn in Massachusetts, New England J. Med. **236**:87-94, 1947.

390. MacGregor, I.: Acute Enteritis in Subtropical Climates, Brit. M. J. **2**: 225, 1946.

391. Kershaw, G. R.: Acute Non-Specific Diarrhea and Dysentery, Brit. M. J. **2**:717-719, 1947.

392. Lindsay, S.: Acute Enterocolitis and Death Resulting from a Markedly Hypertonic Enema, Gastroenterology **7**:364-370, 1946.

The clinical course and almost identical pathologic lesions were reproduced in guinea pigs by enemas of the same composition.

Food Poisoning.—In an epidemic of food poisoning, seven enterotoxic strains of staphylococci were isolated from the throat and feces of patients, from vegetable salad and from cooked ham.[393] Because these organisms were lysed by two lysogenic types of staphylococci and also produced a phage which lysed two cultures of staphylococci, it was concluded that they were identical and that the organism isolated from the food caused the outbreak.

Salmonella Infections.—An efficient and rapid method for the isolation and identification of enteric pathogenic organisms is reported.[394] In a study of 86 sporadic instances of salmonellosis during the period 1941 to 1945, twenty-one serologically identified strains were encountered.[395] Salmonella cholerasuis, Salmonella typhimurium, and Salmonella Oranienberg were recovered in 11, 20 and 16 cases respectively. There was a wide variation in the type of clinical syndromes, which ranged from simple diarrhea to septicemia, and in their severity. Thirteen patients died; 9 were subjected to autopsy. The typhoid-like lesions caused by S. typhimurium are emphasized. Salmonella choleraesuis seemed to produce the clinical picture of sepsis with the greatest regularity. Salmonella Oranienberg produced a relatively mild picture of enteritis, while the condition caused by S. typhimurium tended to be of moderate severity, although there were some fatalities.

An outbreak of gastroenteritis among the pupils of a high school in Habana, Cuba, was caused by S. typhimurium.[396] The source was traced to the water tank, in which a dead rat was found. The outbreaks ceased when the suspected water supply was shut off.

Five cases of Salmonella fever, in all of which the blood culture yielded the organism, were seen in an overseas hospital on Luzon, Philippine Islands.[397] The clinical manifestations varied from a severe systemic infection with pulmonary involvement, cholecystitis and subsequent perforation of the gallbladder to a moderate febrile course with only malaise and headaches. Offending organisms were Salmonella paratyphi A in 3 cases, S. enteritidis in 1, and a member of group C Salmonella in 1.

393. McClure, W. B., and Miller, A. M.: Identification of Identical Strains of Staphylococci in Food Poisoning and Other Infections by Bacteriophage Typing, Canad. M. A. J. **55**:36-39, 1946.

394. Fullgarbe, E. A., and Levant, F. A.: Isolation and Identification of Enteric Pathogens at a Naval Base in North Africa, U. S. Nav. M. Bull. **46**:1398-1402, 1946.

395. Angrist, A., and Mollov, M.: Bacteriologic, Clinical and Pathologic Experience with Eighty-Six Sporadic Cases of Salmonella Infection, Am. J. M. Sc. **212**:336-346, 1946.

396. Reaud, A.: An Outbreak of Gastro-Enteritis Caused by Salmonella Typhimurium, Presumably Water-Borne, South. M. J. **40**:176-180, 1947.

397. Bender, C. E.: Salmonella Fever, Northwest Med. **45**:660-665, 1946.

A case is described [398] in which the etiologic agent was found to be a paracolon organism closely related antigenically to the Q-1030 strain of nonmannitol fermenting dysentery bacilli described in 1943 by Sachs; it was resistant to the sulfonamide drugs but sensitive to streptomycin.

In an infection due to Bacillus paratyphosus B (Salmonella schottmülleri), no benefit was obtained with streptomycin therapy; the organism was demonstrated to be markedly resistant to streptomycin in vitro.[399] In Salmonella suipestifer bacteremia, streptomycin apparently had no effect on the course of the illness, although the organism was somewhat susceptible in vitro.

Bacillary Dysentery.—Experimental bacillary dysentery can be successfully produced in man by ingestion of approximately one billion Shigella organisms in water.[400] A strain of Shigella, extremely virulent for mice, failed to produce clinical infection in man, while other strains of much lower virulence for mice produced moderate or severe dysentery in man. The incubation period in the experimental disease varied from twenty-four to seventy-two hours. Sulfadiazine effectively controlled the dysentery produced by sulfadiazine-susceptible strains of Shigella organisms, and it rapidly suppressed the carrier state.

An epidemic of Sonne dysentery occurred in a large general hospital [401] intermingled with infections for which the cause, after careful investigation, could not be determined but which were similar clinically to those caused by Bacterium sonnei.

Sulfacarboxythiazole (2-sulfanilamido-5-carboxythiazole) was found to be poorly absorbed when given orally, with blood concentrations usually below 1 mg. per one hundred cubic centimeters.[402] The amount of excretion of the drug in the stools varied between 83 and 92 per cent of the amount ingested and that in the urine between 3 and 7 per cent. Satisfactory clinical results were obtained for 44 of 50 patients with diarrhea caused chiefly by dysentery organisms. Toxic reactions developed in 6 cases, including persistent diarrhea in 4, nausea and vomiting in 1 and a nodular cutaneous rash in 1 patient.

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398. Luippold, G. F.: A Paracolon Organism Antigenically Related to the Sachs Q-1030 Bacillus and Associated with Chronic Enterocolitis, Gastroenterology **8**:358-366, 1947.

399. Morgan, H. J., and Hunt, J. S.: Streptomycin in Clinical Practice: A Review and Case Reports, Am. Pract. **1**:73-86, 1947.

400. Shaugnhessy, H. J.; Olsson, R.; Bass, K.; Friewer, F. and Levinson, S. O.: Bacillary Dysentery in Human Volunteers, Yale J. Biol. & Med. **19**:537-546, 1947.

401. Martin, L., and Wilson, M. M.: Sonne Dysentery and Non-Specific Gastroenteritis in a Hospital, Lancet **1**:553-55, 1947.

402. Hirsh, H. L.; Hickman, T. L.; Sweet, L., and Dowling, H. F.: Sulfa Carboxythiazole: Absorption, Excretion, Toxicity, and Therapeutic Results in Bacillary Dysentery and Non-Specific Diarrhea, J. Lab. & Clin. Med. **31**:1305-1313, 1946.

In an epidemic among army personnel on board ship, and subsequently after they landed, Shigella paradysenteriae (Flexner) was recovered repeatedly from the stools.[403] Suggestive evidence is presented to support the view that flies, particularly the "blue bottle" variety, were instrumental in propagating the disease. Treatment consisted of sulfadiazine and supportive therapy along with hospitalization when possible. Morphine was used liberally to control pain and diarrhea. The results in general were extremely good. During this epidemic, and in others among Australian troops, superficial proctitis was observed during the height of the disease and in the convalescent period, but chronic ulcerative colitis did not develop.

Typhoid.—The symptoms in 360 cases of typhoid fever are analyzed.[404] Anorexia was present in 90 per cent, abdominal tenderness in 84 per cent, abdominal distention in 76 per cent, foul breath and sordes in 69 per cent, nausea and vomiting in 54 per cent, intestinal hemorrhage, rarely severe, in 21 per cent, diarrhea at some time in the course of the disease in 43 per cent and constipation in 79 per cent. There were 7 proved instances of perforation (5 ileal and 2 appendical) and 4 instances of probable perforation; meteorism seemed to precede perforation.

Trichinosis.—An outbreak of trichinosis resulting chiefly from the ingestion of uncooked sausage is reported by Shookhoff and his associates;[405] there were no fatalities. Gastrointestinal symptoms occurred in a minority of the cases; the onset of such symptoms was usually simultaneous with the appearance of edema. The commonest initial manifestations were edema of the eyelids and fever. The classic prodromal gastroenteritis occurred in only 7 cases. Eosinophilia was the most constant early laboratory finding. The precipitin test was found more useful than the intradermal test as the reaction to it became positive earlier.

Intestinal Parasites.—Of 59 soldiers in New Guinea studied because of eosinophil counts of 9 per cent or more, 47 (79 per cent) were found to have intestinal helminthic infections. Forty-two (71 per cent) had hookworm disease and 5 (8 per cent) had strongyloidiasis. The high count in 12 (20 per cent) was unexplained.[406] The diagnosis of Strongyloides infection in 4 of 5 cases was made by examination of duodenal fluid; larvae were not found in the feces.

Among 1,114 patients from the South Pacific area, Endamoeba coli was found in 4.9 per cent and Endolimax nana in 19.4 per cent.[407] Of

403. Brown, P. W.: Bacillary Dysentery, Gastroenterology **7**:525-527, 1946.

404. Stuart, B. M., and Pullen, R. L.: Typhoid: Clinical Analysis of Three Hundred and Sixty Cases, Arch. Int. Med. **78**:629-661 (Dec.) 1946.

405. Shookhoff, H. B.; Birnkrant, W. B., and Greenberg, M.: An Outbreak of Trichinosis in New York City, Am. J. Pub. Health **36**:1403-1411, 1946.

406. Denhoff, E.: The Significance of Eosinophilia in Abdominal Complaints of American Soldiers, New England J. Med. **236**:201-206, 1947.

407. Zarrow, M., and Rifkin, H.: Intestinal Parasites Diagnosed at an Army General Hospital, Am. J. M. Sc. **212**:289-293, 1946.

3,415 soldier patients examined for helminth infestation, 13.2 per cent were found to have hookworm. During 1943, the stools of 375 of 1,371 patients (27 per cent) examined for parasites at a Naval Hospital in New Zealand contained parasites, hookworm and Endamoeba histolytica being present in 116 and 97 cases respectively. Eight other pathogens were found in small percentages of the group.[408] Strongyloidiasis responded well to gentian violet medicinal, intraduodenal instillation of a 1 per cent solution being employed in the resistant cases. Hamilton [409] reports the roentgenologic diagnosis of infestation with Taenia saginata; the evacuation roentgenogram clearly showed a long, ribbon-like defect in the ileum.

Amebiasis.—Roberts[410] in an important study has shown that flies, given access to infected material, may transmit E. histolytica cysts in their feces for periods extending from five minutes to at least thirty-one hours.

Miller [411] believes that the over-all incidence of E. histolytica in Canada is approximately 2 per cent but that it may be higher in special groups. An incidence of 13 per cent is reported among 500 servicemen returning from the subtropics; the incidence in three institutions was 20, 23 and 37 per cent respectively.

It is not definitely known whether the drugs commonly used in the treatment of amebiasis exert their influence primarily by inhibition or by destruction of the organisms. Since there is evidence that some degree of resistance to infection occurs, the standard antiamebic drugs and numerous other compounds were tested to determine their amebostatic properties.[412] It was found the paraaminobenzoic acid (PABA) equaled emetine and vioform in this respect; hence, paraaminobenzoic acid and two other compounds (2-n-heptyl-4, 6, diamino-s-trizaine and 2-methyl-4-amino-5-bromomethyl-pyrimidine) deserve a trial if their pharmacologic and toxicologic properties permit. Most antimalarial drugs were found inactive. Vioform and emetine were inhibitory at concentrations of about 0.5 mg. per hundred cubic centimeters (1:200,000). Paraaminobenzoic acid in the same concentration also was inhibitory. As in

408. Willard, J. H.: Intestinal Parasites in Service Personnel in the South Pacific, with Special Reference to the Incidence and Treatment of Strongyloidiasis, Gastroenterology **7**:650-655, 1946.

409. Hamilton, J. B.: Taenia Saginata: A Case Report, Radiology **47**:64-65, 1947.

410. Roberts, E. W.: Part Played by Feces and Vomit-Drop in Transmission of Endameba Histolytica by Massa Domestica, Ann. Trop. Med. **41**:129-132, 1947.

411. Miller, M. J.: Is Amoebiasis a Medical Problem in Canada? Canada. M. A. J. **55**:336-344, 1946.

412. Brackett, S., and Bliznick, A.: The Rate of Multiplication of Endamoeba Histolytica and Its Relation to in Vitro Drug Testing and Possibly to Nutritional Studies, J. Parasitol. **33**:154-165, 1947.

in vitro studies, there is never complete assurance of similar results in vivo; chiniofon, for example, is only mildly active in vitro but effective clinically.

The clinical features of amebiasis and its complications are reviewed by various authors.[413] Lewis [413b] found the reaction to the complement fixation test to be positive in only 7 of 20 cases; in 6 of these the condition was severe. The reaction to the test in 20 carriers was negative. Complications developing in 57 per cent of the overseas patients included ulcerative colitis in 4, granuloma in 3, chronic diarrhea in 3, steatorrhea in 2, amebic abscess in 2, appendicitis in 2 and mucous colitis in 1. Of 5 patients for whom a previous diagnosis of "ulcerative colitis" had been made without the criteria being given, 1 had a history of both amebic and bacillary dysentery, 3 a history of amebic dysentery and 1 a history of undiagnosed dysentery acquired during an epidemic. All were treated with sulfadiazine and 3 with vioform; 4 "recovered," and 1 was transferred elsewhere. The total excretion of fat in twenty-four hours was measured in 26 cases. Normal persons excreted 1.0 to 5.0 Gm. and patients with mild diarrhea 3 to 9 Gm. Nine patients excreted 12 to 80 Gm.; of these, 1 had ulcerative colitis, 1 pancreatogenous steaorrhea and 7 a syndrome closely resembling tropical sprue. All in the latter group had served in New Guinea or in the Philippines for from one to three years. All gave a history of dysentery; amebic infection was proved in 2. The serum protein levels were normal or slightly reduced. The blood calcium or phosphorus levels were below normal in a few cases. The curve for the oral glucose tolerance test tended to be low and flat. The patients responded well to a diet of 40 Gm. of fat, 400 Gm. of carbohydrates and 120 Gm. of protein. Crude liver extract, 5 cc. twice weekly, was given.

Fletcher, Dougan and Sammon [413e] suggest that patients with an enlarged tender liver and with stools not containing amebas be treated with four injections of emetine-hydrochloride to exclude the possibility of an hepatic abscess. A marked decrease in the size and tenderness of the liver occurs with the fourth injection.

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413. (*a*) Murray-Lyon, R. M.: The Aetiology and Diagnosis of Amoebiasis, Edinburgh M. J. **54**:65-75, 1947. (*b*) Lewis, R. A.: Enteric Infections and Their Sequelae, New England J. Med. **235**:571-581, 1946. (*c*) Kenamore, B.: Chronic Diarrhea in Military Personnel Returning from the Tropics, Gastroenterology **7**:528-532, 1946. (*d*) Morton, T. C.: Diagnosis of Chronic Dysentery in Service Personnel, Brit. M. J. **2**:890-893, 1946. (*e*) Fletcher, J. P.; Dougan, A. A., and Sammon, Q. M.: Amoebiasis, Canad. M. A. J. **55**:278-283, 1946. (*f*) Hayward, G. W.: Amoebiasis in Italy, Brit. M. J. **13**:457-459, 1946. (*g*) Klatskin, G.: Observations on Amebiasis in American Troops Stationed in India, Ann. Int. Med. **25**:773-788, 1946. (*h*) Cameron, J. D. S.: Amoebiasis, Edinburgh M. J. **54**:76-89, 1947. (*i*) Elsom, K. A.; Roger, A. M., and Wood, F. C.: Amebiasis: Observations in an Army General Hospital in India, Gastroenterology **8**:135-153, 1947.

Klatskin [413g] found that the routine administration of moderate doses (6 grains [0.36 Gm.] in six days) of emetine hydrochloride together with the intensive use of chiniofon and carbarsone retention enemas yielded a relapse rate of 5.6 per cent in 162 consecutive cases; in contrast a rate of 9.6 per cent was observed in 355 consecutive cases in which carbarsone and an iodine preparation were given if the patients were asymptomatic and an additional 4 grains (0.25 Gm.) of emetine hydrochloride in four days if they were symptomatic. Among more than 500 patients treated with emetine hydrochloride only one serious complication, severe myocarditis, occurred; the routine therapy erroneously was not carried out in this instance.

In a series of patients treated by Cameron [413h] in the early days of the war when emetine hydrochloride was the only amebicidal drug available, "cures" were obtained in about one third and temporary remission with subsequent relapse in one third and no effect was noted in the rest. Emetine hydrochloride was found to be ineffective in many conditions of the intestinal type, attributable presumably to the fact that the amebas in avascular necrotic and fibrous tissue were less accessible. A drop in blood pressure was the most common initial sign of toxicity to emetine hydrochloride, followed by an irregular pulse, heart block and myocardial changes. Neuritis with pain, weakness and paralysis were the chief nervous manifestations. No single amebicidal drug was found to be entirely effective. Combinations of emetine hydrochloride, diodoquin, carbarsone and succinylculfathiazole yielded the best results. Penicillin was given in secondary or concomitant bacterial infections. Hepatic abscesses rarely required surgical drainage. "Medical" aspiration was necessary when the abscess was large and fluctuant; others receded and disappeared with proper systemic treatment. Introduction of emetine hydrochloride into abscess cavities served no useful purpose.

Elsom and his associates [413i] report that the reponse to emetine hydrochloride was definite, prompt and sometimes dramatic. Four patients with amebic abscess, not responding to medical therapy, were treated with aspiration under direct observation at laparotomy.

Albright and Craig,[414] warning that the sources of amebic infection will increase with the return of troops from endemic areas overseas, emphasize also that the term "carrier state" is misleading, for the presence of the parasite in any form means invasion of the tissue. All asymptomatic "carriers" should be treated with emetine hydrochloride and an enteric drug such as chiniofon or carbarsone.

Amebiasis involving the cecum may simulate all types of cecal and appendical lesions, according to Wilbur and Camp.[415] The high mortality

414. Albright, E. C., and Gordon, E. S.: Present Status of the Problem of Amebiasis, Arch. Int. Med. **79**:253-271 (March) 1947.

415. Wilbur, D. L., and Camp, J. D.: Amebic Disease of the Cecum: Clinical and Radiological Aspects, Gastroenterology **7**:535-548, 1946.

from surgical therapy makes it imperative to distinguish amebiasis of the cecum from appendicitis. Smyth [416] calls attention to similarities between carcinoma and ameboma.

Various writers [417] emphasize further the importance of combining emetine hydrochloride and other drugs such as carbarsone, chiniofon and vioform in the therapy of amebiasis.

Dack and Moloshok [417e] describe toxic cardiac manifestations after emetine hydrochloride was given in total dosages ranging from 7 to 22 grains (0.45 to 1.32 Gm.). In some cases electrocardiographic abnormalities did not appear until one to two weeks after treatment had ended, and they persisted in some for two months or more. In a study of the role of secondary bacterial pathogens in amebic colitis, Ellenberg [418] treated 59 patients with 27 Gm. each of sulfadiazine over a five day period, with the result that in 98 per cent the condition either cleared or improved considerably; necrotic sloughs and diffuse inflammatory mucosal reactions, as viewed proctoscopically, disappeared, leaving clean-based ulcers. Siguier [419] reports that the simultaneous administration of penicillin, sulfonamide drugs and emetine hydrochloride to 100 patients resulted in permanent eradication of the amebas in 50 per cent; relapses occurred in the other 50 per cent at much longer intervals than those observed after the administration of emetine hydrochloride alone.

Bingham [420] discusses the surgical management of various complications of amebiasis such as pericolic infections, appendical involvement and amebic abscess of the liver.

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416. Smyth, M. J.: Confusion of Amoeboma with Carcinoma, Lancet **2**:376-377, 1946.

417. (*a*) Murgatroyd, F.; Hargreaves, W. H.; Lovibond, J. L.; Somervell, T. H.; Morgan, C. N.; Wright, A. D., and Hunt, A. H.: Use of Medicaments in Disease of the Colon and Rectum, Proc. Roy. Soc. Med. **39**:541-550, 1946. (*b*) Karl, M. M., and Sloan, F. R.: The Management of Amebiasis, Ann. Int. Med. **25**:789-798, 1946. (*c*) Arnett, J. H.: Treatment of Carriers of Endamoeba Histolytica and Other Protozoa with Carbarsone, Chiniofon and Vioform, Am. J. M. Sc. **213**:608-610, 1947. (*d*) Monat, H. A., and Hertner, J. E.: Intractable Amebiasis, a Warning, with Report of a Case, Mil. Surgeon **99**:310-312, 1946. (*e*) Dack, S., and Moloshok, R. E.: Cardiac Manifestations of Toxic Action of Emetine Hydrochloride in Amebic Dysentery, Arch. Int. Med. **79**:228-238 (Feb.) 1947. (*f*) Rail, G. A.: Comparative Effect of Drugs Used in Treatment of Amebiasis, J. Trop. Med. **50**:3-12, 1947.

418. Ellenberg, M.: Amoebiasis: The Role of Bacteria in Symptomatology: I. Sigmoidoscopic Findings in Symptomatic and Asymptomatic Cases; II. The Effect of Sulfadiazine on Symptoms and Sigmoidoscopic Findings, Am. J. Digest. Dis. **13**:356-360, 1946.

419. Siguier, F.: La methode d'Hargraves blanc dans le traitement des amibiases chroniques et à rechutes en milien tropical d'àpres 100 observations, Arch. d. mal. de l'app. digestif **36**:33-62, 1947.

420. Bingham, D. L. C.: The Treatment of Some Surgical Complications of Amoebiasis, Canad. M. A. J. **55**:341-344, 1946.

Schistosomiasis.—Faust,[421] testing the effect of cold on eggs of Schistosoma japonicum, found that a considerable proportion of eggs would survive and hatch under conditions approximating the cold season of South China; a smaller percentage would survive the winter in Central China and extremely few would remain viable in endemic areas in Japan. Alves and Blair [422] describe the preparation and use of a cercarial antigen for intradermal testing of the skin which gives a higher proportion of positive reactions than are revealed by repeated microscopic examinations. The cutaneous test is helpful also in assessing the efficacy of therapy. However, Faust [423] considers the demonstration of the eggs to be the only known method of specific diagnosis; skilled, experienced technicians and repeated examinations are required. In the late chronic stage, eggs are frequently fewer in number, immature and degenerate; in this stage the intradermal antigen reaction should be positive.

Among 495 soldiers who had been hospitalized overseas and treated with at least one course of "fuadin" (sodium antimony III biscatechol-2, 4-disulfonate) or tartar emetic or both five to nine months previously, 156 were still passing eggs.[424] In the early part of the study, the direct smear method accounted for 88 per cent of the positive reactions and the gravity sedimentation technic for 38 per cent; 12 per cent were detected by the latter technic only. The direct smear, in combination with one or more procedures for sterilizing sedimentation, detects more infected stools than any one method alone.

Martin and others [425] found no constant or significant changes in the blood sedimentation rate or in the plasma protein level; eosinophilia was of slight significance. Competent examination of at least three successive stools is necessary.

Among 481 patients studied by Mason and others,[426] recurrent epigastric cramps and tenderness were the most frequent complaints on admission to the hospital. There was little evidence of hepatomegaly and

421. Faust, E. C.: The Effects of Cold Temperature on the Eggs of Schistosoma Japonicum, J. Parasitol. **33**:134-137, 1947.

422. Alves, W., and Blair, D.: Diagnosis of Schistosomiasis: Intradermal Test Using a Cercarial Antigen, Lancet **2**:56-560, 1946.

423. Faust, E. C.: Schistosomiasis Japonica: Its Clinical Development and Recognition, Ann. Int. Med. **25**:585-600, 1946.

424. Hesselbrock, W. B.; Lippincott, S. W.; Palmer, E. D.; Henderson, E. W., and Pauls, F. P.: A Study of Various Methods of Stool Examination in the Diagnosis of Schistosomiasis Japonica, Am. J. Clin. Path. **17**:197-204, 1947.

425. Martin, W. B.; Graziani, J. G.; Collins, J., and Lincicum, D. R.: Chronic Infestation with Intestinal Parasites in an Engineer Battalion with Particular Reference to Schistosoma Japonicum, South. M. J. **39**:885-888, 1946.

426. Mason, P. K.; Daniels, W. B.; Paddock, F. K., and Gordon, H. H.: Schistosomiasis Japonica: Diagnosis and Treatment in American Soldiers, New England J. Med. **235**:179-182, 1946.

splenomegaly, although these were reputed to be the most frequent complications in the native population where the infestation was acquired. Repeated examination of the stools by more than one method was necessary to demonstrate the ova. Persistent eosinophilia was suggestive of the disease. In similar studies [427] a known relapse rate of 42 per cent was observed. Proctoscopic signs consisted of 1 to 2 mm. yellowish nodules, isolated or in clusters, with or without induration or superficial ulceration. Ova may be recovered in these nodules.

Cerebral manifestations are described by Tillman.[428] Prodromal symptoms, occurring within thirty-nine to one hundred days from the day of first possible exposure, consisted of fever, cough, weakness and malaise, urticarial eruption, headache, abdominal pain, pain in the chest, chills and diarrhea. In every instance there was a lucid interval of eleven to twenty-eight days between these symptoms and the onset of neurologic disturbances. Usually the cerebral phase began insidiously, but occasionally it was abrupt. Aphasia, amnesia, blocking, confusion, disorientation, defective memory and coma were outstanding. Spasticity, occasional early flaccidity changing to spasticity, rigidity, hyperreflexia, pathologic reflexes and loss of superficial reflexes were common to all patients. In 5 cases transient disturbances of the third, fourth and sixth cranial nerves were present, and in 2 there was questionable involvement of the facial nerve. Motor paralysis was characteristic, involving one or more limbs, but a lesion of the lower motor neuron was not observed. Sensation was not affected.

Lippincott and his associates [429] studied the effect of treatment with antimony. Of 33 patients given "fuadin" 27 (82 per cent) were again passing eggs within three months or less. These 27 were again treated with "fuadin"; 24 were passing eggs again in three months' time or less. Of 59 patients treated with tartar emetic, 11 (19 per cent) were passing eggs within three months or less. Both drugs produced an average plasma antimony level of about 100 micrograms per liter after 0.75 Gm. of antimony had been given in about five weeks' time; the concentration at all

427. Winkenwerder, W. L.; Hunninen, A. V.; Harrison, T.; Billings, F.; Tremains, C.; Douglas, G., and Maier, J.: Studies on Schistosomiasis Japonica: II. Analysis of Three Hundred and Sixty-Four Cases of Acute Schistosomiasis with Report of Results of Treatment with Fuadin in One Hundred and Eighty-Four Cases, Bull. Johns Hopkins Hosp. **79**:406-435, 1946. Mason, P. K.; Daniels, W. B.; Paddock, F. K., and Gordon, H. B.: Latent Phase of Asiatic Schistosomiasis, Arch. Int. Med. **78**:662-678 (Dec.) 1946.

428. Tillman, A. J. B.: Schistosomiasis Japonica with Cerebral Manifestations: Report of Seven Cases, Arch. Int. Med. **79**:36-61 (Jan.) 1947.

429. Lippincott, S. W.; Ellenbrook, L. D.; Rhees, M., and Mason, P.: A Study of the Distribution and Fate of Antimony When Used as Tartar Emetic and Fuadin in the Treatment of American Soldiers with Schistosomiasis Japonica, J. Clin. Investigation **26**:370-378, 1947.

stages was higher in the cells than in the plasma. For several hours after administration of the drug, a higher concentration in the blood cells was found in the group given tartar emetic than in the group given "fuadin." Since the adult worms are known to infest erythrocytes, the question is raised whether the higher blood cell concentration of antimony obtained with tartar emetic may not be responsible for the superior therapeutic efficiency of this drug as compared with "fuadin."

APPENDIX

Arterial Supply.—Careful dissections in 60 injected cadavers revealed a single appendical artery in 42; in only 19 did the course correspond with the description found in textbooks.[430]

Appendicitis.—Bohrod [431] points out that the development of appendical lymphoid tissue, with narrowing of the lumen, closely parallels the incidence of acute appendicitis with respect to the characteristic age and sex distribution. The lymphoid tissue reaches its maximum development in the first decade and is better developed in the male. When the muscularis fully develops in the second decade, the lumen becomes small. Appendicitis results from obstruction of the lumen. Moses [432] reports that traction on the appendix or distention of the lumen will reproduce the cramping, poorly localized pains characteristic of early appendicitis. Early appendicitis is regarded as a miniature "blind loop" form of intestinal obstruction. If the obstruction is not relieved, venous congestion ensues, with the outpouring of an exudate into the lumen and the wall and around the exterior of the appendix; persistence of this process results in arterial occlusion, with resultant perforation or gangrene.

Kay and Lockwood,[433] in a study of experimental appendical peritonitis, found that there were no quantitative hematologic changes of prognostic significance although alterations in the prothrombin time were of suggestive value.

In a series of cases reported by Tashico and Zinninger [434] the average delay in hospitalization for acute unruptured appendicitis was 26.6 hours; for acute appendicitis with perforation it was 75.6 hours. The mortality

430. Shah, M. A., and Shah, M.: The Arterial Supply of the Vermiform Appendix, Anat. Rec. **96**:457-460, 1946.

431. Bohrod, M. G.: The Pathogenesis of Acute Appendicitis, Am. J. Clin. Path. **16**:752-760, 1946.

432. Moses, W. R.: Appendicitis: A Clinico-Pathological Study, South. M. J. **39**:902-906, 1946.

433. Kay, J. H., and Lockwood, J. S.: Experimental Appendiceal Peritonitis: I. The Prognostic Significance of Certain Hematologic Factors, Especially the Prothrombin Time, Surgery **20**:56-71, 1946.

434. Tashico, S., and Zinninger, M. M.: Appendicitis: A Review of Nine Hundred and Thirty-Six Cases at the Cincinnati General Hospital, Arch. Surg. **53**:545-563 (Nov.) 1946.

rate was 5.3 per cent among Negroes and 2.6 per cent among white persons.

Hurwitt [435] emphasizes the need for laparotomy in the presence of persisting signs and symptoms ordinarily associated with acute appendicitis despite the preexistence or coexistence of other diseases that may produce abdominal complaints, such as pneumonia, tonsillitis, infections of the upper respiratory tract, mastoiditis, chronic glomerulonephritis, myocardial infarction, inguinal hernia, diabetes mellitus and syphilis of the central nervous system.

Simpson [436] discusses the clinical features of acute appendicitis in persons over 60 years of age. The mortality rate for this group is approximately 25 to 30 per cent.

Intestinal obstruction roentgenologically simulating cancer of the rectosigmoid proved at operation to be due to appendicitis with pelvic peritonitis.[437]

In a group of 50 cases of appendical peritonitis, treated without drainage and with immediate appendectomy in 22, the administration of 100,000 units of penicillin every two hours for several days resulted in the recovery of all but 1 patient.[438]

In an analysis of 5,540 cases of acute appendicitis at Cook County Hospital since 1928, Meyer, Requarth and Kozoll [439] found that from 1928 to 1932 the mortality rate was 1.1 per cent when perforation had not occurred and from 1944 to 1945 it was 0.78 per cent. When perforation had occurred, it was 26.4 per cent in the earlier period and 13.9 per cent in the later one, the reduction being attributed chiefly to chemotherapy. In cases of acute appendical abscess the nonoperative (Ochsner) treatment yielded results much superior to those obtained by the operative treatment, the mortality rates being 18 and 4.2 per cent respectively in the early period and 8.5 and 3.1 per cent in the later period. Jackson [440] reports 15 cases of perforative appendicitis with peritonitis or abscess formation in which the appendix was removed, sulfathiazole employed intraperitoneally and the incision closed without drainage; there were no deaths, although a secondary intraperitoneal abscess in 1 case required

435. Hurwitt, E. S.: Acute Appendicitis Occurring During the Course of Other Diseases, New England J. Med. **236**:20-23, 1947.

436. Simpson, D. G.: Acute Appendicitis in the Aged, Brit. M. J. **2**:986-989, 1946.

437. Courty, M. A.: Pseudo-cancer recto-sigmoidien du a une appendicite pelvienne, Arch. d. mal. de l'app. digestif **35**:74-77, 1946.

438. Crile, G., Jr.: Peritonitis of Appendiceal Origin Treated with Massive Doses of Penicillin, Surg. Gynec. & Obst. **83**:150-162, 1946.

439. Meyer, K. A.; Requarth, W. H., and Kozoll, D. D.: Progress in the Treatment of Acute Appendicitis, Am. J. Surg. **72**:830-840, 1946.

440. Jackson, A. S.: Non-Drainage and Early Ambulation in Cases of Perforative Appendicitis, Arch. Surg. **54**:644-655 (June) 1947.

drainage. The treatment of peritonitis is further discussed by Crile [441] and by Brown.[442]

Streptomycin is given the credit for a dramatic recovery from peritonitis caused by a colon bacillus subsequent to ureterolithotomy in a patient with ureteral calculi and a purulent renal infection due to Escherichia coli. The condition was not influenced by the administration of sulfonamide drugs and penicillin.[443] Bacilli apparently were fully eliminated from the peritoneal cavity but not from the urinary tract, although there was no obstruction.

Mucocele.—A mucocele of the appendix suspected clinically and diagnosed roentgenologically was found at operation.[444] Miller [445] reports 5 cases in which a mucocele of the appendix was originally diagnosed as appendicitis; perforation occurred in another instance.[446]

Taenia Saginata.—Two cases in which Taenia saginata were present in the appendix are described.[447]

Carcinoid.—Of 29 carcinoids of the appendix, metastatic lesions were found in 3.[448] Early removal is more frequent than in carcinoid of the stomach because on account of the symptoms of appendicitis the appendix is removed; the diagnosis is often overlooked.

Carcinoma.—A primary adenocarconoma of the appendix was associated with the development of a mucous fistula.[449]

COLON

Parasympathetic Innervation.—Lannon and Weller,[450] in a study of the nerve supply to the distal half of the large intestine in 9 infants and 9 adults (all Bantu), state that the parasympathetic nerves arise from the

441. Crile, G., Jr.: Peritonitis, Am. J. Surg. **72**:859-864, 1946.

442. Brown, M. J.: Combined Penicillin and Sulfonamide Treatment of Peritonitis, Am. J. Surg. **73**:56-61, 1947.

443. Muellner, S. R., and Rutenberg, A.: The Use of Streptomycin in Colon Bacillus Peritonitis, New England J. Med. **235**:327-328, 1946.

444. Euphrat, E. J.: Roentgen Features of Mucocele of the Appendix, Radiology **48**:113-117, 1947.

445. Miller, D.: Mucocele and Myxoglobulosis of the Appendix, S. Clin. North America **27**:337-343, 1947.

446. Longo, O. F.: Mucocele apendicular perforado, Bol. y trab., Acad. argent. de cir. **30**:863-870, 1946.

447. Clark, H. C.: Taenia Saginata in the Appendix, Am. J. Surg. **7**:128-129, 1946. Rossi, A. A., and Bruzzoni, N. R.: A Case of Appendicitis Caused by Taenia Saginata, Prensa méd. argent. **33**:2085-2086, 1946.

448. D'Ingianni, V.: Carcinoid of the Appendix with Metastasis, New Orleans M. & S. J. **99**:158-161, 1946.

449. Crile, G. and Glenn, C. G.: Primary Adenocarcinoma of the Appendix with Development of Mucus Fistula, U. S. Nav. M. Bull. **47**:328-330, 1947.

450. Lannon, J., and Weller, E.: The Parasympathetic Supply of the Distal Colon, Brit. J. Surg. **34**:373-376, 1947.

second and third sacral segments and are distributed directly to the rectum and the descending colon. They communicate with the hypogastric plexuses but do not follow the paths of the blood vessels. The authors point out that in the application of these results in operations on the colon periarterial stripping of the inferior mesenteric artery should not lead to parasympathetic dysfunction of the colon and that resection of the rectum and the lower pelvic colon should not destroy the parasympathetic supply to the colon.

Hepatodiaphragmatic Interposition.—Starr [451] reports the roentgenologic demonstration of colon between the liver and the diaphragm.

Megacolon.—The clinical and roentgenologic features and the early development of megacolon in the newborn are described by Ehrenpreis.[452] The process is apparently due to a disturbance of innervation; improper evacuation is considered primary and dilatation secondary.

Twenty-eight cases of primary megacolon observed in the past twenty-five years at the Lahey Clinic are described by Swarts.[453] In 20 it was congenital, in 2 acquired and in 6 indeterminate. The most constant symptoms were constipation and abdominal pain. Twenty-one patients were managed medically, with good results in 16. Seven patients were subjected to sympathectomy, colectomy or both, with excellent results in only 1. Sympathectomy has been disappointing; colectomy is considered the procedure of choice if medical management fails. The regular use of enemas and the avoidance of laxatives are outlined as basic principles of treatment. Impactions are a constant source of trouble, for which small enemas of magnesium, glycerin and water are recommended. Mecholyl bromide, 0.1 to 0.2 Gm., may be occasionally of benefit.

Scott and Serenati [454] present a somewhat different view, dividing megacolon into four types for which diverse therapeutic procedures are indicated: congenital organic obstruction requiring some type of plastic procedure, neurogenic dysfunction responding diagnostically and therapeutically to spinal anesthesia or requiring lumbar sympathectomy, functional obstruction (abnormal length of sigmoid) relieved by resection of the redundant loop with or without sympathectomy and extrinsic metabolic difficulties necessitating replacement therapy. However, these authors agree that most patients should first be subjected to a conservative medical regimen consisting of colonic irrigations, mineral oil, mild catharsis in rare instances, low roughage diet and drugs.

451. Starr, E.: Hepatodiaphragmatic Interposition of the Colon with Gastric Hypertrophy, Am. J. Roentgenol. **56**:22-26, 1946.

452. Ehrenpreis, T.: Megacolon in the Newborn: A Clinical and Roentgenological Study with Special Regard to the Pathogenesis, Acta chir. Scandinav. 1946, supp. 112, pp. 1-403.

453. Swarts, J. M.: Primary Megacolon, Gastroenterology **8**:519-525, 1947.

454. Scott, W. J. M., and Serenati, O. J.: Megacolon: Mechanisms and Choice of Treatment, Surgery **20**:603-618, 1946.

Functional Disorders.—Prolonged proctoscopic observations were made by Almy and Tulin [455] on 7 healthy young men. When under stress from mechanically produced headache or from pain caused by immersion of the forearm in ice water, the subjects manifested a bodily reaction comprising hypertension, sweating, sighing, pallor of the skin and changes in colonic function. Increased motor activity of the lower part of the sigmoid was regularly present; significant engorgement of the mucosa was usually seen and occasionally an increased secretion of mucus. These phenomena appeared to be independent of the quality of the emotional reactions of the subject. The emotional conflicts consisted of resentment toward the experimenters, concern about self preservation, desire to comply and self reproach. Nausea, usually associated with spasm of the sigmoid, was absent in 2 subjects predominantly resentful.

The psychosomatic aspects of gastrointestinal disorders are discussed by a number of writers.[456] Dakin points out that lack of special psychiatric training or of time should not deter the physician from learning the emotional disturbances in every patient and from treating these factors with psychologic technics.

Functional gastrointestinal disorders accounted for a large part of the disability from medical causes in the United States Army.[457] Hospitalization, with prolonged investigation and medical treatment, had an adverse effect. Prompt and direct attention to the personality disturbance, with a minimum of emphasis on medical study and organic therapy, resulted in a significant saving in manpower, a considerable decrease in hospitalization and great benefit to the patients. The reviewers agree in principle but they are reluctant to minimize the importance of medical study; both types are important.

Ulcer of the Cecum.—A benign ulcer of the cecum clinically simulated appendicitis. At operation a malignant growth was suspected, and a hemicolectomy was performed.[458] Ileocolic intussusception occurred at the site of a nonspecific cecal ulcer.[459]

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455. Almy, T. P., and Tulin, M.: Alterations in Colonic Function in Man Under Stress, Experimental Production of Changes Simulating the "Irritable Colon," Gastroenterology **8**:616-626, 1947.

456. Dakin, M. J.: The Psychosomatic Approach in General Practice, M. Clin. North America **31**:213-222, 1947. Paster, S.: General Aspects of Psychosomatic Medicine, Rev. Gastroenterol. **14**:391-402, 1947. Savitt, R. A.: Gastrointestinal Disorders in Military and Civilian Life, ibid. **14**:402-409, 1947. Portis, S. A.: The Gastroenterological Aspects of Psychosomatic Medicine, ibid. **14**:409-419, 1947. Gibb, W. T., Jr.: Functional Derangement of Digestion, Am. Pract. **1**:542-548, 1947.

457. Halsted, J. A.: Functional Gastrointestinal Disorders: Lessons Learned from Military Medicine, New England J. Med. **235**:747-754, 1946.

458. Cromar, C. D. L.: Benign Ulcer of the Caecum, Am. J. Digest. Dis. **13**:230-232, 1946.

459. Blum, L.: Nontumid Ileocolic Intussusception in an Adult: Report of a Case with Cecal Ulcer, S. Clin. North America **17**:355-360, 1947.

Volvulus.—According to Gardiner,[460] volvulus of the cecum is far more common than has hitherto been supposed. In 50 per cent of the cases it occurs in patients between the ages of 20 and 40, but the process is frequently found in older persons. Males seem to be more often affected than females, the proportion being 3 to 1. Failure of the normal fixation of the cecum and persistence of its mesentery leave the cecum and the ascending colon with a variable degree of mobility and liable to torsion. Exertion and strenuous occupations are precipitating factors; other exciting causes include trauma, pregnancy, dietetic errors, gaseous distention and violent purgation. The usual symptoms are pain and tenderness in the right iliac fossa shifting to the center of the abdomen, with immediate or subsequent gaseous distention and obstruction; the temperature and pulse often remain normal throughout. A plain roentgenogram of the abdomen is of great value and often establishes the diagnosis. Treatment consists of laparotomy, with derotation and fixation if the intestine is viable or with hemicolectomy if it is gangrenous. Volvulus of the sigmoid, an uncommon cause of intestinal obstruction, usually occurs only if the sigmoid is dilated, long and redundant.[461] Demonstration of a corkscrew-like arrangement of the mucosa in spot roentgenograms is pathognomonic.

Diverticulosis and Diverticulitis.—Several papers have appeared.[462] Anderson [462b] describes an instance of cecal diverticulitis with perforation and peritonitis, the hundredth case to be reported. The patient recovered after closure of the diverticulum and sulfonamide therapy. Ballinger [462c] reviews gastrointestinal roentgenologic examinations made in 1,000 consecutive cases. Diverticula were present in 115 (11.5 per cent); in 98 (9.8 per cent) they were in the colon, in 16 (1.6 per cent) in the duodenum and in only 1 (0.1 per cent) in the esophagus. Of the 98 cases of colonic diverticula, evidence of diverticulitis was present in 25.

Morton [462d] describes the typical clinical picture of diverticulitis: a corpulent sedentary person, middle aged or older, with a history of constipation, is seized suddenly with cramping, colicky pain in the lower abdomen, diarrhea and increasing constipation. This is frequently fol-

460. Gardiner, R. H.: Volvulus of the Caecum, Brit. M. J. **1**:83-87, 1947.

461. Ritvo, M., and Golden, J. L.: The Roentgen Diagnosis of Volvulus of the Sigmoid with Intestinal Obstruction, Am. J. Roentgenol. **56**:480-488, 1946.

462. (*a*) Galambos, A., and Mitelmann-Galambos, W.: Diverticulosis and Diverticulitis of the Colon, Rev. Gastroenterol. **13**:171-194, 1946. (*b*) Anderson, L.: Perforated Diverticula of the Cecum with Peritonitis, Proc. Staff Meet., Mayo Clin. **21**:465-469, 1946. (*c*) Ballinger, W. M.: Diverticula of the Digestive Tract, South. M. J. **39**:897-902, 1946. (*d*) Morton, J. J., Jr.: Diverticulitis of the Colon, Ann. Surg. **124**:725-745, 1946. (*e*) Schlotthauer, H. L.: Familial Diverticulosis of the Colon: Report of Seven Cases in One Family of Nine Persons, Ann. Surg. **124**:497-502, 1946. (*f*) Cohen, S. E., and Matthews, B. L.: Dissecting Diverticulitis of the Colon, Surgery **20**:823-827, 1946.

lowed by nausea, vomiting, distention, fever and tenderness in the lower quadrants, usually the left, where a mass often is palpable. Moderate leukocytosis is the rule. About 20 per cent have occult blood in the stool. The complications include obstruction, abscess, perforation, peritonitis and formation of fistula. In 17 of 111 patients carcinoma was also present. There were 39 perforations, with 12 deaths. Diverticulitis with spasm is a self-limiting disease, necessitating only rest, supportive therapy and dietary restriction in most instances. Proximal colostomy occasionally may be necessary. Diverticulitis with complications almost invariably is a serious disorder, demanding expert surgical intervention.

Diverticulosis of the colon was found in all the male members of a white family of 9 (7 brothers and 2 sisters) of ages ranging from 49 to 68 years.[462e] A type of diverticulum of the colon is described which begins as a herniation of the lumen into the wall of the bowel and burrows its way along the wall, termed "dissecting intramural diverticulitis."[462f]

Ulcerative Colitis.—In an excellent article, Ginsberg and Ivy[463] critically review the evidence pertaining to the cause of the disease. Acute lesions of the colon have been produced by the intravenous injection of diplostreptococci, streptococci, B. coli, Bacillus dysenteriae and presumably a virus. Cook has shown experimentally that acute ulcers may be produced and maintained or relapses elicited by apical dental infections, using the diplostreptococcus of Bargen. This work has not been repeated. Observations on Bacillus necrophorum suggest that it may play a role in the chronicity of the disease. Mechanical trauma, vascular injuries caused by contraction of the muscularis or by capillary poisons, sclerosing solutions or allergenic substances may cause acute lesions tending to heal rapidly. The colitides of tuberculosis, amebiasis, bacillary dysentery and lymphogranuloma are separate entities. Though emotional factors may play a role in exacerbation of symptoms and may be related to the onset of the disease, there is a paucity of evidence showing that ulcerative colitis is the end result of functional, vascular or neurotropic disturbance.

In a comparative clinical study of 22 cases of regional enteritis and 67 cases of idiopathic ulcerative colitis, Weinberg and his associates[464] noted no significant difference in the age distribution or the sex incidence. Hemorrhage was the first manifestation in a case of acute ulcerative colitis.[465] Proctoscopic examination was not diagnostic, but roentgen studies revealed a narrowed descending colon and sigmoid, with pronounced distortion of the mucosal pattern.

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463. Ginsberg, R. S., and Ivy, A. C.: The Etiology of Ulcerative Colitis: An Analytical Review of the Literature, Gastroenterology **7**:67-90, 1946.

464. Weinberg, B. J.; Sorter, H., and Necheles, H.: Regional Enteritis and Idiopathic Ulcerative Colitis: A Clinical Study, Am. J. Digest. Dis. **13**:346-350, 1946.

465. Jobb, E.: Unusual Initial Onset of Ulcerative Colitis with Exsanguinating Bowel Hemorrhage, Gastroenterology **7**:483-488, 1946.

A case of acute fulminating colitis, with peritonitis, extensive loss of the bowel wall and death five weeks after the onset, is reported;[466] therapy had consisted of the administration of plasma, blood, sodium sulfadiazine and large quantities of solutions containing sodium schoride and sugar. Five similar cases from the literature are analyzed; all the patients died in less than nine weeks. Exploratory operation had been performed in all, including ileostomy, suture of a perforation, drainage of an abscess, cecostomy and appendicostomy in individual cases.

Ricketts and Palmer,[467] reporting an incidence of one or more complications in 31 per cent of 206 cases, classify the complications into five groups: (1) those involving the colon itself, (2) those involving adjacent structures, (3) those distant from the colon, (4) those resulting from deficient nutrition and (5) a miscellaneous group. The complications in the first group included polyps in 21, stricture in 8, obstruction in 6 and carcinoma in 3. Hemorrhage occurred frequently, but there was no fatality from this. In the second group internal or external fistulas were found in 9 and perforation with peritonitis in 7. Complications distant from the colon were lesions of the skin and mucosal surface in 22, arthritis in 12, venous thromboses in 4, hepatitis in 1 and septic infection in 27. There were 3 cases of infantilism in a subgroup of 23 children. Peripheral neuritis was observed in 3 patients.

Anemia was present in 71 of 109 cases reported by Pollard and others,[468] it was hypochromic and microcytic in 58 and normocytic in 13. Many factors apparently contributed to the development of the anemia, including chronic hemorrhage, inadequate intake or defective absorption of food, deficient nutrition, toxemia and exacerbations of the disease.

Five instances of hepatic cirrhosis, observed by Tumen and others [469] among 151 cases of ulcerative colitis, were attributed to nutritional deficiencies (anorexia, hypermotility, poor absorption and loss in rectal discharges), with absorption of toxic substances as a possible additional factor.

Cattell and Boehme,[470] emphasizing the importance of malignant degeneration, found approximately 75 cases in a review of the literature

466. Chisholm, T. C.: Acute Fulminating Ulcerative Colitis with Massive Perforation and Peritonitis, Arch. Surg. **53**:462-476 (Oct.) 1946.

467. Ricketts, W. E., and Palmer, W. L.: Complications of Chronic Non-Specific Ulcerative Colitis, Gastroenterology **7**:55-66, 1946.

468. Pollard, H. M.; Block, M. and Bachrach, W. H.: Causes and Management of Anemia Associated with Chronic Ulcerative Colitis, J. A. M. A. **134**: 341-346 (May 24) 1947.

469. Tumen, H. J.; Monaghan, J. G., and Jobb, E.: Hepatic Cirrhosis as a Complication of Chronic Ulcerative Colitis, Ann. Int. Med. **26**:542-553, 1947.

470. Cattell, R. B., and Boehme, E. J.: The Importance of Malignant Degeneration as a Complication of Chronic Ulcerative Colitis, Gastroenterology **8**:695-710, 1947.

and described 9 additional instances. The lesions are highly malignant and metastasize early. The average duration of symptoms before the diagnosis of a malignant process was nine years. The lesions were in the cecum in 1, in the hepatic flexure in 1, and in the rectum and rectosigmoid in 7. Histologically, there were three adenocarcinomas, three carcinomas of the simplex type and three mucinous carcinomas. All 9 patients were subjected to operation; 4 underwent a resection, palliative only in 2 instances since local or distant metastasis was present. There were no operative deaths; the 2 patients without metastasis are living and well five and one-half years and twenty months respectively after operation. The other 7 patients died from various causes.

By means of "biographic anamnesis," a detailed life history was obtained from 6 patients with ulcerative colitis which demonstrated that the onset of the disease and its recurrences were related to emotional trauma resulting in a specific internal conflict.[471] The author formulates this conflict as an acute love loss, combined with humiliation and a feeling of inferiority, and regards it as the cause of the colitis. Four of the 6 patients improved after supportive psychotherapy.

West [472] reports 3 cases relieved by brief psychotherapy and discusses the principles of such treatment. The experiments of Lium and Porter (1939) wherein colonic ulcerations were produced in twenty-four hours by sustained colonic muscular spasm and healing induced after relaxation for ten to fourteen days are recalled. It is hypothesized that in some cases of ulcerative colitis anxiety causes muscular spasm and mucosal changes in an organ previously rendered susceptible by either a psychologic or a physical sensitization or both. While the diarrheal response to frank anxiety is well known, much of the anxiety of these patients is unconscious. Deep anxiety over problems of emotional aggressiveness characterizes ulcerative colitis.

Of 55 patients treated with succinylsulfathiazole and observed for two years, 74.5 per cent had a complete remission of symptoms, 7.3 per cent improved and 18.2 per cent did not improve.[473] Thirty-nine patients (71 per cent) had no complicating toxic or systemic manifestations, and thus their condition was classified as mild. It was in this group that most of the remissions occurred.

Thirty-seven patients with ulcerative colitis were treated with 2-(p-nitro-benzenesulfonamido)-thiazole, or nisulfazole, in doses of 4 to 6

471. Groen, J.: Psychogenesis and Psychotherapy of Ulcerative Colitis, Psychosom. Med. **9**:151-174, 1947.

472. West, R.: Psychotherapy of Ulcerative Colitis, Lancet **2**:899-903, 1946.

473. Collins, E. N., and Hewlett, J. S.: Succinyl Sulfathiazole (Sulfasuxidine) in the Treatment of Chronic Ulcerative Colitis: A Report of Fifty-Five Cases Followed Two Years; Its Value by Retention Enema in Early Cases, Gastroenterology **7**:549-554, 1946.

Gm. initially, gradually reduced to 1 to 2 Gm. daily.[474] Thirty-four patients were reported to have recovered, i.e., to be symptom free and passing not more than two to three well formed stools daily; 3 were improved. Ten known relapses occurred, four of these during an infectious disease. No untoward effects were observed in patients taking 1 to 2 Gm. daily for several months; 2 patients took 2 Gm. daily for seventeen and twenty months respectively.

The use of sulfonamide drugs and antibiotics is discussed comprehensively by Bargen.[475] Azosulfamide ("neoprontosil") is considered the most effective drug in chronic ulcerative colitis, although toxic reactions occur. Sulfathiazole, sulfadiazine, sulfaguanidine, succinylsulfathiazole ("sulfasuxidine") and phthalylsulfathiazole ("sulfathaladine") have been found effective in selected cases. The administration of several of the sulfonamide drugs may be more effective than the use of one alone. The best results with penicillin have been obtained in the acute fulminating forms; perhaps the doses, already large, should be even greater. In the few patients to whom streptomycin was administered preliminary results were not encouraging.

Improvement apparently occurred in 3 patients after thiouracil had been given and in 1 after methyl thiouracil.[476]

Twenty-one patients with ulcerative colitis were treated with preparations of small intestinal mucosa of the hog.[477] Two dried preparations are compared; one in which enzymal activity was retained proved ineffective, and the other caused apparent remission of symptoms in 9 cases. The physiologic basis for this therapy is obscure. The authors wisely point out that the evaluation of any therapy in this disease is difficult and requires a careful assessment of adequate control data.

Lahey[478] recommends early ileostomy for patients not responding to medical management. The mortality rate in his experience has been reduced from 26 to 2 per cent. Cave[479] reports that among 101 patients with intractable ulcerative colitis treated surgically by ileostomy and by partial or complete colectomy there were twenty immediate or early fatalities. Of the 81 survivors, 50 have been followed over a period

474. Major, R. H.: The Nisulfazole Treatment of Chronic Ulcerative Colitis, Am. J. M. Sc. **1**:485-490, 1946.

475. Bargen, J. A.: The Use of the Newer Sulfonamides and Antibiotics in Intestinal Diseases, M. Clin. North America **30**:919-931, 1946.

476. Martin, L.: Treatment of Ulcerative Colitis with Thiouracil, Lancet **2**:944-946, 1946.

477. Gill, A. M.: Treatment of Ulcerative Colitis with Intestinal Mucosa, Proc. Roy. Soc. Med. **39**:512-519, 1946.

478. Lahey, F. H.: Earlier Ileostomy in Severe Ulcerative Colitis, Surg., Gynec. & Obst. **85**:230-232, 1947.

479. Cave, H. W.: Late Results in the Treatment of Ulcerative Colitis, Ann. Surg. **124**:716-724, 1946.

ranging from one to ten years. The fecal stream has been successfully reestablished in 2 patients by ileosigmoidostomy. Eleven patients underwent primary ileosigmoidostomy; lesions of the terminal ileal segment, requiring further resection developed in 2 patients, 1 of whom died. Acute ileus and ileal prolapse were not infrequent complications. Sudden collapse from loss of salt occasionally occurred. Forty of the patients are leading an active, useful life.

Crohn and his associates [480] comprehensively review 77 cases of so-called right-sided colitis. The age distribution was similar to that in usual ulcerative colitis or ileitis. The average age was 27.3 years; the youngest patient was 6 and the oldest 60 years of age. There were 45 women and 32 men. Pure "right-sided colitis" involving the cecum and the ascending colon was observed in 22 instances. The transverse colon and the descending colon alone were regionally involved in 16 cases. In the remaining 39 cases the proximal colon from the cecum to the sigmoid was involved either continuously or intermittently by "skip" lesions. Associated involvement of the terminal end of the ileum was noted in 33 cases. Intestinal obstruction occurred in 2, fistula in 15, perirectal abscesses without fistulas in 4, internal fistula in 1 and fecal fistulas opening on the abdominal wall in 2. Fever was the most outstanding general manifestation of the disease, being present in 49 of the 77 cases. Monoarticular, but more commonly polyarticular, involvement was frequent. The prognosis of "right-sided colitis" is considered "good," with a survival rate of 84 per cent. Among 55 patients treated surgically there were 9 deaths. Of the 46 surviving operation, only 3 experienced subsequent involvement of the rectum and required ileostomy; 2 of these died. The authors regard segmental colitis as an entity different from ulcerative colitis in its clinical course, its manifestations and its response to surgical therapy.

Lymphopathia Venereum.—The etiology, symptoms, diagnosis and treatment are discussed by Wright, Freeman and Bolden.[481] In the prestricture stage sulfonamide compounds seem to have some beneficial effect, but it is doubtful if drugs can permanently prevent extension of the process in all cases. Penicillin has not been of value. Surgical treatment is necessary once a fibrous stricture of any considerable extent has developed. Five instances of carcinoma superimposed on the granulomatous lesion are described in addition to 27 case histories. Savignac [482] reports complete rectal obliteration.

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480. Crohn, B. B.; Garlock, J. H., and Yarnis, H.: Right-Sided (Regional) Colitis, J. A. M. A. **134**:334-338 (May 24) 1947.

481. Wright, L. T.; Freeman, W. A., and Bolden, J. V.: Lymphogranulomatous Strictures of the Rectum, Arch. Surg. **53**:499-544 (Nov.) 1946.

482. Savignac, M. R.: Un nouveau cas d'obliteration complete d'une stenose inflammatoire du rectum, Arch. d. mal. de l'app. digestif. **35**:77-80, 1946.

Polyps.—During a nineteen month period, 1,031 women who considered themselves well submitted to sigmoidoscopic and roentgenologic examinations.[483] Nineteen polyps were found in 18 persons. No symptoms characterized the group; none of the 19 polyps was palpable by rectal examination or visible after a barium enema. Microscopic sections of tissue taken from these lesions were studied independently by three pathologists; complete agreement was recorded in regard to only three specimens. Polypoid disease of the colon, according to Buie,[484] is of two main types: (*a*) discrete polypoid outgrowths, usually sessile, with normal intervening mucosa and (*b*) a diffuse hyperplastic involvement, with polyps of all types, sizes and shapes.

In a study of the incidence and distribution of adenomas of the large intestine in 1,460 consecutive autopsies, Helwig [485] found that the incidence increases with age, reaching a maximum (24 per cent) in the eighth decade. The over-all incidence in Negroes was 2.7 per cent and that in white patients 10.5 per cent. Adenomas were slightly more frequent in men than in women. A single adenoma was found in 80 of 139 patients, and two or more tumors were noted in the rest. Adenomas are considered true neoplasms rather than a reaction to a diffuse inflammatory process. Swinton [486] shares this opinion.

Generalized polyposis of the colon in a woman aged 22 was treated, in sequence, by electrocoagulation of polyps, ileosigmoidostomy and partial colectomy.[487] Rectal hemorrhages recurred three years later, necessitating a two stage resection of the colon and rectum. Microscopic examination revealed malignant degeneration of two of the polypi. Copello and Ramos Mejia [488] report a multiple polyposis involving both the small and the large intestine.

Dixon and Benson [489] treated most of their 19 patients with polypoid disease by performing ileosigmoidostomy at the first stage and subsequently by fulguration of the remaining polypi in the rectum and rectosigmoid.

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483. Ortmayer, M.: Biologic Characteristics of Non-Palpable, Non-Symptomatic Solitary Polyps of the Rectum, J. Nat. Cancer Inst. **7**:387-393, 1947.

484. Buie, L. A.: Remarks Concerning Malignant Lesions, Polypoid Disease and Diverticula of the Terminal Portion of the Large Intestine, S. Clin. North America **26**:968-980, 1946.

485. Helwig, E. B.: The Evolution of Adenomas of the Large Intestine and Their Relation to Carcinoma, Surg. Gynec. & Obst. **84**:36-49, 1947.

486. Swinton, N. N.: The Significance of Mucosal Polyps of the Colon and Rectum, S. Clin. North America **27**:675-680, 1947.

487. Charrier, J.; Hillemand, J., and Hartman, L.: Treatment of Generalized Essential Rectocolic Polyposis, Arch. d. mal. de l'app. digestif **36**:5-16, 1947.

488. Copello, O., and Ramos Mejia, M. M.: Poliposis difusa del intestino delgado y del grueso, Bol. y trab., Acad. argent. de cir. **30**:635-646, 1946.

498. Dixon, C. F., and Benson, R. E.: Total and Subtotal Colectomy with Review of Seventy-Two Cases, S. Clin. North America **26**:949-967, 1946.

Lipoma.—Runyeon [490] reports 2 submucous lipomas and reviews 121 similar ones. Two submucous lipomas originating in the ileocecal valve and in the ascending colon produced intermittent intussusception.[491] A subserous lipoma grossly simulated carcinoma.[492]

Carcinoma.—McLaughlin [493] describes carcinoma of the cecum in association with acute appendicitis, the twelfth instance to be recorded in the literature.

The sex incidence in 50 cases of carcinoma of the cecum was approximately uniform.[494] The average age was 47.8 years, the youngest patient being 19 and the oldest 72. The average duration of symptoms before operation was 10.1 months. Pain was present in 92 per cent and was the first symptom in 74 per cent. It was located in nearly all cases in the right lower abdominal quadrant, beginning usually as a dull ache and progressing to a cramping colicky pain. Weight loss was pronounced in 46 per cent, the average loss being 25 pounds (11.3 Kg.). Constipation and diarrhea were noted in 8 patients; some change in bowel habits occurred in 38 per cent. Ten per cent of the patients noted a mass in the right lower quadrant before presenting themselves for examination; in 2 the mass was the first indication of the disease. Anemia was a presenting complaint in 4, all having been previously treated with iron and liver.

Cole [495] presents evidence that earlier diagnosis, better preoperative and postoperative care and improved surgical technics have decreased the mortality rate. However, antibiotics are not a substitute for careful surgical treatment.

Forty-eight authentic cases of carcinoma of the large bowel, excluding the rectum and sigmoid, in patients 16 years of age or less are reviewed by Johnston.[496] Colloid carcinoma is ten times more frequent in children; hence palpable masses are commonly found. A carcinoma of the transverse colon in a 15 year old boy is reported.[497]

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490. Runyeon, F. G.: Submucous Lipoma of the Colon, New York State J. Med. **46**:2272-2276, 1946.

491. Pack, G. T., and Booher, R. J.: Intussuscepting Submucous Lipoma of the Right Colon, S. Clin. North America **27**:361-372, 1947.

492. Threadgill, F. D.: Intestinal Lipoma Simulating Carcinoma of the Sigmoid Colon, Am. J. Surg. **73**:398-400, 1947.

493. McLaughlin, E. F.: Carcinoma of the Cecum in Association with Acute Appendicitis, Am. J. Surg. **72**:585-593, 1946.

494. Jarvis, J. L., and Cayer, D.: Cancer of the Cecum: A Review of the Clinical Features, Am. J. Digest. Dis. **14**:95-98, 1947.

495. Cole, W. H.: Carcinoma of the Colon, Illinois M. J. **91**:229-238, 1947.

496. Johnston, J. H., Jr.: Carcinoma of the Colon in Childhood and Adolescence, Am. J. Surg. **73**:703-712, 1947.

497. Fishback, H. R.: Carcinoma of the Transverse Colon in a Fifteen-Year-Old Boy: Case Report with Short Summary of the Literature, Radiology **48**:168-171, 1947.

Two carcinomas were found in 102 cases of diverticulosis.[498] Of 726 cases of cancer of the colon, multiple lesions occurred in 3 per cent.[499] The diagnosis depends on preoperative roentgen examinations and on careful exploration of the entire colon at the time of operation.

An encapsulated, semicystic, papillary mucous cystadenocarcinoma, weighing 8 pounds (3.6 Kg.) and measuring 50 cm. in diameter, was removed from the right groin of a 60 year old white man.[500] Though no involvement of the lumen of the colon was detected on palpation and grossly the tumor was entirely extraperitoneal, it was thought to have arisen from the cecum or the proximal portion of the ascending colon. Two instances of carcinoma of the colon simulating linitis plastica are reported.[501]

Five interesting cases of multiple carcinomas of the rectosigmoid are described.[502] Lahey [503] points out that although the clinical features of carcinoma of the colon and rectum may suggest an inoperable lesion exploratory operation should not be discouraged in view of the unpredictability of the rapidity of growth and metastatic involvement; this is particularly true of lesions of the right side of the colon, many of which appear inoperable clinically yet are found to be readily resectable.

Sarcoma and Miscellaneous Lesions.—A lymphosarcoma in a polyp on the posterior wall of the rectum was removed by fulguration; the patient was well five years later.[504]

Gotlieb [505] records an unusual case of intersigmoid hernia diagnosed roentgenologically. The diagnostic features consisted of considerable distention of proximal loops of small intestine, normal passage of barium apart from a temporary stop at the sigmoid at the level of the herniation, obvious extrinsic pressure resembling a poorly defined filling defect in the sigmoid but varying with change in the position of the patient. normal

498. Oren, B. G.: Diverticulosis Coli with Coexisting Carcinoma of the Rectosigmoid, South. M. J. **40**:304-308, 1947.

499. Mider, G. B.: Multiple Invasive Carcinomas of the Large Intestine, Surgery **20**:744-748, 1946.

500. Castro, A. F.; Bargen, J. A.; Clagett, O. T., and Dockerty, M. B.: Cystic Tumor of Right Groin: A Complication of Carcinoma of the Colon, Gastroenterology **8**:95-100, 1947.

501. Karstens, H. C., and Bargen, J. A.: Carcinoma of the Colon Simulating Linitis Plastica: Report of Two Cases, Proc. Staff Meet., Mayo Clin. **22**:231-259, 1947.

502. D'Allaines, F., Bensaude, A., and Motoñeos, G.: Contribution à l'étude des cancers multiples primitives du rectum, Arch. d. mal. l'app. digestif. **35**:392-403, 1946.

503. Lahey, F. H.: Prognosis of Patients with Carcinoma of the Colon, Rectosigmoid and Rectum, S. Clin. North America **27**:670-674, 1947.

504. Harris, F. I., and Feigen, G. M.: Lymphosarcoma of the Rectum: Five Year Cure Following Local Removal, Am. J. Surg. **72**:277-279, 1946.

505. Gotlieb, G. G.: A Case of Intersigmoid Hernia with Illustrations of X-Ray Appearances, Brit. J. Radiol. **19**:429-431, 1946.

emptying of the colon by evacuation, localized tenderness on palpation and an isolated gas bubble in the arrested coil of small intestine, seen more distinctly in the erect position and separable from the sigmoid by manual pressure.

Cattell and Colcock [506] report seven unusual lesions of the large intestine consisting of cystic disease of the bowel, lymphosarcoma of the cecum, nonspecific cicatrizing regional ulcerative colitis, endometriosis of the colon, leiomyosarcoma, lymphogranuloma venereum and basal cell carcinoma of the rectum.

Colostomy.—Jones and Kehm [507] describe the management of the patient with a permanent colostomy opening and direct attention to the various complications which may ensue, including difficulty in irrigation, prolapse or constriction of the opening, hernia, bleeding and diarrhea.

DISEASES OF THE ANUS AND RECTUM

Congenital Malformations.—Rosenblatt and May [508] report 20 cases of malformation. A duplication of the rectum which assumed the characteristics both of a cyst and of a diverticulum was treated successfully by marsupialization.[509]

Pruritus Ani.—Swinton [510] points out that the scratch-itch syndrome is a basic factor in the background of a large number of patients with an intractable anal pruritus. In intractable cases the initial precipitating factor may have disappeared or have become so altered that it is no longer significant. The possible precipitating causes are numerous and include physiologic, infective, allergic, psychogenic and mechanical factors. The physical examination should include an anoscopic and proctoscopic examination. Adequate rest, relaxation and relief from tension are required. When first seen, patients should be given a brief but intelligent discussion of the subject and routinely advised to wash themselves often with cotten moistened in warm water; toilet tissue and soap should be eliminated. The ensuing dryness and cleanliness and the avoidance of trauma will definitely control most of the mild forms. Surgical intervention should be limited to removal of sources of infection and the correction of obvious local disease. Injections of alcohol relieve the scratch-itch syndrome but should be reserved for the severe cases. The importance of psychogenic

506. Cattell, R. B., and Colcock, B. P.: Unusual Lesions of the Large Intestine, S. Clin. North America **27**:651-658, 1947.

507. Jones, T. E., and Kehm, R. W.: Management of the Permanent Colostomy, Cleveland Clin. Quart. **13**:198-202, 1946.

508. Rosenblatt, M. S., and May, A.: Malformation of the Anus and Rectum, Surg. Gynec. & Obst. **83**:499-506, 1946.

509. Cogswell, H. D., and Thompson, H. C., Jr.: Duplication of the Rectum, Am. J. Dis. Child. **73**:167-174, (Feb.) 1947.

510. Swinton, N. W.: Pruritus Ani, New England J. Med. **236**:169-172, 1947.

mechanisms should never be overlooked. Gardner [511] devised a surgical treatment consisting of Gabriel's hemorrhoidectomy modified by the removal of a much larger portion of the skin around the anus; the results are reported as excellent for all 35 patients so treated. The reviewers are of the opinion that careful adherence to Swinton's program and also to that prescribed by Shapiro and Rothman (*Gastroenterology* 5: 155-168, 1945) will almost completely eliminate any need for Gardner's operation.

Miscellaneous Conditions.—Granet [512] considers coccygodynia to be due in most cases to reflex spasm of the coccygeal muscles; tender bursas over the levator ani may be partially responsible for the pain. Anorectal abscesses are reviewed by Wenzel.[513] Bacon and his associates,[514] in a comprehensive discussion of diseases of the rectum, conclude that strictures of all types are best treated by perineal excision preceded by a permanent colostomy. Mere anal stenosis is successfully corrected by attaching mobilized mucous membrane to the marginal wound.

A large enterogenous cyst arising from the rectum produced a nontender 12 by 11 cm. cystic mass containing 600 cc. of thick tenacious material; the intestinal wall had undergone fibrosis, hyalinization, deposition of calcium and pressure atrophy of the epithelial lining.[515]

Twenty-five cases of carcinoma of the anus treated by irradiation, with adequate follow-up, are reviewed by Meland,[516] with the conclusion that irradiation offers reasonable expectation of complete recovery, with added hope of sphincter control.

MISCELLANEOUS GASTROINTESTINAL SUBJECTS

Preoperative and Postoperative Care.—Among a series of 250 patients treated preoperatively and postoperatively with either "sulfasuxidine" (succinylsulfathiazole), "sulfathaladine" (phthalylsulfathiazole) or both there were no instances of demonstrable or fatal peritonitis, fecal fistulas, or wound disruptions.[517] The effectiveness of these drugs is at-

511. Gardner, C. M.: Pruritus Ani, Canad. M. A. J. **55**:259-262, 1946.

512. Granet, E.: Proctalgias and Allied Non-Inflammatory Perianal Dyscrasias: Coccygodynia, Proctalgia Fugax, Neurogenic Pruritus Ani, Am. J. Digest. Dis. **13**:330-333, 1946.

513. Wenzel, J. F.: Anorectal Abscesses, Am. Surg. **72**:517-525, 1946.

514. Bacon, H. E.; Fleming, J. P.; Pedlow, L. L.; Smith, C. H.; Holoman, M. B., and Rowe, R. J.: The Diagnosis and Treatment of Diseases of the Anorectum, Am. J. Med. **1**:257-267, 1946.

515. Custer, B. S.; Kellner, A., and Escue, H. M.: Enterogenous Cysts: Report of Case Involving the Rectum, Ann. Surg. **124**:508-518, 1946.

516. Meland, O. N.: Carcinoma of the Anus, Am. J. Roentgenol. **57**:199-204, 1947.

517. Poth, E. J.: Sulfasuxidine and Sulfathalidine in Surgery of the Colon, South. M. J. **40**:369-375, 1947.

tributed to their antibacterial action, to the mechanical removal of gas and feces, to the reduction of distention and to the earlier administration of a high protein diet.

Amino acids administered orally or parenterally may be used as a protein substitute although palatability in the oral preparations is yet to be obtained.[518] Caution is recommended in the rapid intravenous administration. Plasma is expensive and lacks two essential amino acids.

Peritoneum.—Ivanissevich and Defazio[519] report a rare case of gelatinous disease of the peritoneum.

Retroperitoneal Tumors.—Cattell and Warren [520] describe five retroperitoneal lipomas. The surgical removal of these tumors is attended by a 20 to 25 per cent mortality, death occurring from hemorrhage and shock due to their enormous size and their close relation to the great vessels and other retroperitoneal viscera.

Among ninety-five retroperitoneal tumors, the most frequent types were sarcoma (14), fibrosarcoma (18) and undifferentiated neoplasms (23).[521] Metastasis and local recurrences occurred in about 30 per cent of the cases. Adams [522] reports four interesting mesenteric tumors.

Abscess.—Occasionally, gas formation is the most significant roentgenologic sign of an abdominal abscess, and it often aids in the differentiation from tumor and hematoma.[523] Gas formation in abdominal abscesses does not necessarily indicate the presence of an infection due to Clostridium welchii and related bacteria, since it may be caused by such organisms as aerobic streptococci and E. coli.

Trauma.—Crohn [524] discusses this important subject and presents illustrative cases.

Military Gastroenterology.—According to Chamberlin,[525] functional disorders, epidemic diarrhea and peptic ulcer caused the greatest numbers

518. Remington, J. H.; Bargen, J. A., and Lundy, J. S.: Amino Acid Alimentation in Gastro-Intestinal Diseases, Gastroenterology **7**:442-449, 1946.

519. Ivanissevich, O., and Defazio, F.: Maladie gelatineuse du péritoine, Semana méd. **53**:554-566, 1946.

520. Cattell, R. B., and Warren, K. W.: Retroperitoneal Lipoma, S. Clin. North America **27**:659-665, 1947.

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of gastrointestinal disabilities in the service. The incidence of peptic ulcer among combat troops was not higher than that in civilian life. Patients with functional digestive disorders constituted about one third of all those admitted to general hospitals for symptoms related to the digestive tract.

Macroglossia.—Baber [526] describes an instance of amyloid macroglossia, the fourth to be reported in England. As in previous cases, the deposits were located chiefly in the tongue, skeletal muscles and heart.

Abdominal Pain.—The various theories and controversial issues concerning the mechanisms of abdominal pain are reviewed by Schutz.[527] Stickney,[528] in a discussion of acute abdominal pain, points out that the differentiation of visceral and root pain by paravertebral block or local infiltration with anesthetic agents is not reliable since such procedures interrupt the visceroparietal reflex and, therefore, may abolish the pain of visceral disease as well as that of the nerve roots.

Moore [529] defines abdominal epilepsy as a disorder characterized by bouts of paroxysmal abdominal pain due to hypermotility of the bowel, provoked by abnormal nervous impulses originating presumably in the premotor and postmotor cortex or in the diencephalon. Various organic conditions may serve as trigger mechanisms for the epileptic discharge. In general, such mechanisms involve biophysiochemical disturbances such as hypoglycemia and cerebral anoxia.

Allergy.—Gastrointestinal allergy, according to Chobot,[530] is most frequently seen in children up to the age of 5. It is encountered in the adult most often in cases of urticaria and angioedema. There are two mechanisms of allergic reaction. In the immediate type symptoms follow ingestion of food within fifteen minutes to an hour. There are positive cutaneous reactions and skin-sensitizing antibodies are present in the blood. In the delayed reaction, symptoms follow ingestion of food after one to seventy-two hours. There are no positive cutaneous reactions and no circulating skin-sensitizing antibodies in the blood. Ninety-eight per cent of the food allergies in children undergo spontaneous involution. Chobot points out that too often vague symptoms of indigestion are

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promptly labeled as evidence of allergy without further evidence, a statement with which the reviewers are in complete accord.

Meningococcic Meningitis with Hemorrhage.—Gray and Talisman [531] report fulminating meningococcic meningitis accompanied with a massive gastrointestinal hemorrhage; the patient recovered, and the exact source of the bleeding was not determined.

Abdominal Apoplexy.—Spontaneous rupture of a splenic arterial vessel, or so-called abdominal apoplexy, is reported and the records of 35 cases analyzed.[532]

Hunt and Weller [533] describe an instance of rupture of an abdominal aortic aneurysm into the gastrointestinal tract and briefly review 40 similar cases previously reported. The third portion of the duodenum is most frequently involved. Important clinical criteria are an abdominal tumor, almost always pulsating, in 60 per cent of cases, roentgen signs in 75 per cent and pain in the abdominal or lumbar region. Hematemesis is usually terminal.

Actinomycosis.—The clinical manifestations and the treatment of abdominal actinomycosis are reviewed on the basis of 5 cases.[534] The appendix is the site of origin in most instances. The portal of entry is thought to be the alimentary tract. Peritonitis occurs only if there is perforation of the intestine. Prolonged chemotherapy (sulfadiazine) combined with adequate surgical care is presented as the treatment of choice.

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531. Gray, I., and Talisman, M. R.: Massive Gastrointestinal Hemorrhage in Fulminating Meningococcus Meningitis (Waterhouse-Freiderichsen Syndrome) with Recovery, New York State J. Med. **47**:1389-1391, 1947.

532. Tanna, J. F.: Abdominal Apoplexy, Am. J. Surg. **73**:132-136, 1947.

533. Hunt, H. H., and Weller, C.: The Syndrome of Abdominal Aortic Aneurysm Rupturing into the Gastrointestinal Tract, Am. Heart J. **32**:571-578, 1946.

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Book Reviews

Experimental Catatonia: A General Reaction-Form of the Central Nervous System and Its Implications for Human Pathology. By Herman Holland de Jong, M.D. Price, $4. Pp. 225. Baltimore: Williams & Wilkins Company, 1945.

The experimental production of catatonia in animals by the use of bulbocapnine was first described by the author and Baruk in 1930. The present book represents an extension and an expansion of that significant research. A variety of substances are now known to produce catatonic signs. The first part of this book consists of detailed and extensive protocols of numerous experimental studies. Catatonia was induced by means of drugs, asphyxiation, centrifugation, surgical occlusion of the carotid arteries, audiogenic stimulation and other methods.

The implications for human pathology, with particular reference to catatonic schizophrenia, are presented in the second part of the book.

Dr. de Jong concludes that experimental catatonia is analogous to epileptiform seizures in that both conditions represent nonlocalized diffuse reactions of the central nervous system. He offers the suggestion that cellular asphyxiation may be responsible for the onset of catatonic signs.

He believes that schizophrenia is primarily an "organic" disease, the mental symptoms being secondary phenomena. He cautiously suggests that there may be a toxic etiologic agent in this disease since "only alterations of the function of the liver and the intestine proved capable of producing experimental catatonia," lesions of the other organs having no such effect. Abnormal reactions to liver function tests on catatonic schizophrenics suggested the possibility of primary hepatic damage resulting in the formation of a toxic protein metabolite which may produce cellular anoxia in the nervous tissues and resultant catatonic signs.

This book is skillfully written and authoritative, and it represents stimulating research by an internationally known scientists. It should be of great interest to physicians and to research workers concerned with the physiologic approach to the baffling problem of the etiology of schizophrenia.

Nogle respirationsfysiologiske undersogelser ved lungetuberkulose: Thoracoplastikkens indflydelse paa lungevolumen den alveolaere ventilation belyst ved fractioneret alveoleluftanalyse. By Ulf Gad. Pp. 159. Copenhagen: G. E. C. Gads Forlag, 1941.

This monograph, written in Danish with an English summary, presents studies in preoperative and postoperative lung volumes and composition of alveolar air on patients with pulmonary tuberculosis subjected to thoracoplasty. The first of three chapters deals with the effect of thoracoplasty on lung volume in 51 subjects. Vital capacity was determined spirometrically and compared with results derived from West's formula. Residual air was determined by the hydrogen dilution method. Patients with tuberculosis usually had lowered total capacities and often relatively high residual fractions preoperatively. Postoperatively, the

vital capacity was further reduced, but in 24 per cent the residual air was increased. He found patients to be dyspneic on exertion if vital capacity was less than half of the calculated normal amount. Incidentally, the use of roentgenologic planimetry in estimation of lung volume was found unreliable because of wide individual variation.

The second chapter gives the extremely variable results of testing 78 patients for "mixing capacity" after the manner of Lundsgaard and Schierbeck.

The last chapter reports fractional gas analyses on expired and alveolar air both preoperatively and postoperatively with the use of Sonne and Nielsen's apparatus after single inspirations of pure hydrogen. Hydrogen content on expiration decreased more rapidly than normally, and the rate of decrease varied with the severity of the pulmonary tuberculosis. On the other hand, since oxygen values in expired air were more nearly normal in these subjects, the author assumes that blood flow must have decreased in the poorly ventilated parts of the lungs (62 patients).

The author concludes that dyspnea in his patients was due to changed lung volumes and to disturbed alveolar ventilation and that dyspnea might have been worse but for compensating alterations in alveolar blood perfusion. Ingenious charts are included.

Since this work was published, direct measurements of ventilation capacity have shown that vital capacity taken alone can be no criterion of ventilation. Gray, Cournand and others have further clarified the subject of pulmonary function, developing and applying clinically useful tests in studies made on normal and on diseased subjects.

This study is one of the first to compare strictly preoperative and postoperative testing in large series of cases of thoracic disease requiring surgical treatment; it deserves the attention of those who are interested in respiratory physiology and thoracic diseases.

The Foot and Ankle: Their Injuries, Diseases, Deformities and Disabilities. By Philip Lewin, M.D. Third edition. Price $11 (buckram). Pp. 847, with 389 illustrations. Philadelphia: Lea & Febiger, 1947.

Whether it is logical to assemble in one massive book everything to be known about the foot is an interesting question for discussion. For example, should arthritis of the foot be discussed in a book on arthritis or in a book on the foot? Do the circulatory disturbances in the foot belong under the same covers with bunions or are the latter best dealt with in an orthopedic treatise? Be this as it may, Dr. Lewin's book is now in its third edition, so that there is evidently a place for topographic medicine of this sort. The volume is a handsome one, well and profusely illustrated, and there is a lengthy bibliography. The reviewer is glad to have the book on his shelves.

Maladies et syndromes rares ou peu connus. By A. Aimes, M.D. Pp. 208, with 26 illustrations. Paris: Masson & Cie, 1946.

As the title of this monograph indicates, most of the rare medical syndromes are discussed. The syndrome is defined and the characteristics summarized. It is an extremely useful book.